Official Journal of the Interstate Postgraduate Medical Association

Volume 23, Number 4 **APRIL 1958**

Postgraduate Medicine

UNIVERSITY OF MICHIGAN
SEP
MEDICAL

In This Issue

The 'New' Respiratory Viruses . . . . . Robert J. Huebner

Drug Therapy of Cardiac Arrhythmias . . . . William R. Wilson and James W. Culbertson

Electrolytes and Nutrition . . . . . T. S. Danowski

Estrogenic Therapy in Gynecology . . . . . Daniel G. Morton

The Nephrotic Syndrome in Adults . . . . . Morton H. Maxwell

Hepatic Function . . . . . Hans Popper

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Postgraduate Medicine

Volume 23 · Number 4

APRIL · 1958

OFFICIAL JOURNAL OF THE INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION

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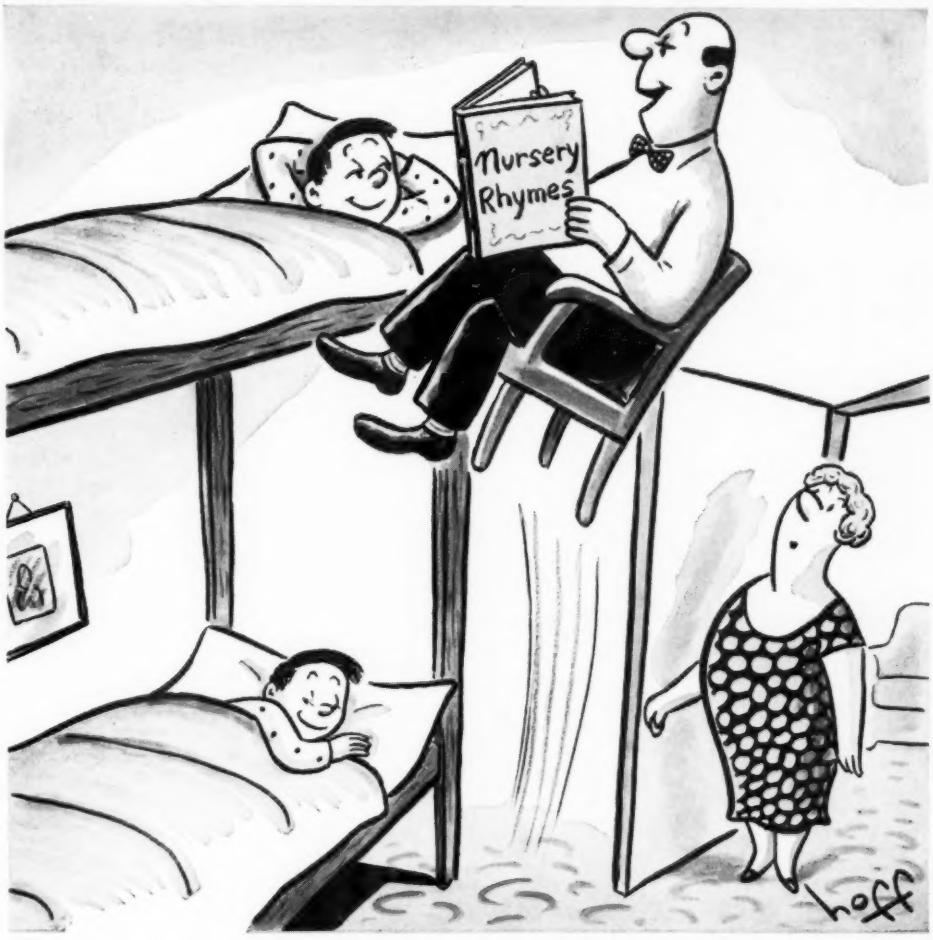

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• BLOODY SPUTUM ACCOMPANYING COUGH

Q. A 39 year old unmarried woman complains of a slight, productive, chronic cough which began in 1946. Occasionally, especially four or five days before menstruation, she has noticed slight streaks of blood in her expectoration. She has presented no other symptoms and her weight has remained constant. Her grandfather died of pulmonary tuberculosis, but she denies any contact with him. An x-ray of the lungs in 1948, subsequent fluoroscopic examinations, and a radiograph in 1956 gave negative results for tuberculosis. In 1953 she was given daily injections of 1 gm. of streptomycin until 70 vials had been used, but her cough showed no improvement. Her sputum has not been examined, nor have any other laboratory tests been made. The physician who did the radiography suspects bronchiectasis. Can you suggest further laboratory studies? What is your diagnosis and prescribed treatment?

M.D.—Philippines

A. The question did not state that a diagnosis has been made in this case. Cough and expectoration are symptoms of many conditions. Slight streaks of blood in the sputum four or five days before menstruation could be vicarious menstruation; however, other causes should be considered.

Since tuberculosis has been suspected, the first step should be a tuberculin test. If the patient does not react to 0.1 or 1 mg. of original tuberculin or corresponding amounts of purified protein derivative, tuberculosis is almost certainly not present. If she does react to this test, it indicates that she has tuberculous lesions containing tubercle bacilli somewhere in her body. The lesions may be microscopic in size and of no present clinical significance, or some may have evolved to larger size. The tuberculin reaction is specific for the presence of tuberculosis in some stage of its evolution. The only other specific finding in this disease is the recovery of tubercle bacilli. If this patient reacts to tuberculin, her sputum should be examined. It is not unusual for a person with clear x-ray films of the lungs to have tubercle bacilli recovered from sputum or stomach washings. In such cases the organisms may originate in lymph nodes or other lesions which have eroded into bronchi.

The fact that the x-ray films of her chest gave negative results does not preclude tuberculosis. The usual x-ray film allows one to visualize only about 75 per cent of the lungs. Gross lesions may be present in the remaining 25 per cent. Lesions in the visualized portion of the lungs must be not only macroscopic in size but they also must have consistency to obstruct x-rays if they are to cast visible shadows on films. It is never correct, therefore, to assume that tuberculosis is not present on the basis of a clear x-ray film of the chest.

Whether or not tubercle bacilli are recovered in this case, bronchoscopy is indicated to determine whether any visible lesions are present in the trachea, bronchi or larger ramifications. A bronchoscopist may be able to determine the source of the material that is being expectorated with reference to the bronchus or the ramifications from which it is draining. Bronchography should be done on the side from which material is draining to determine whether bronchiectasis is present and, if so, to what extent.

Prescribed treatment must await the diagnosis.

(Continued on page A-26)

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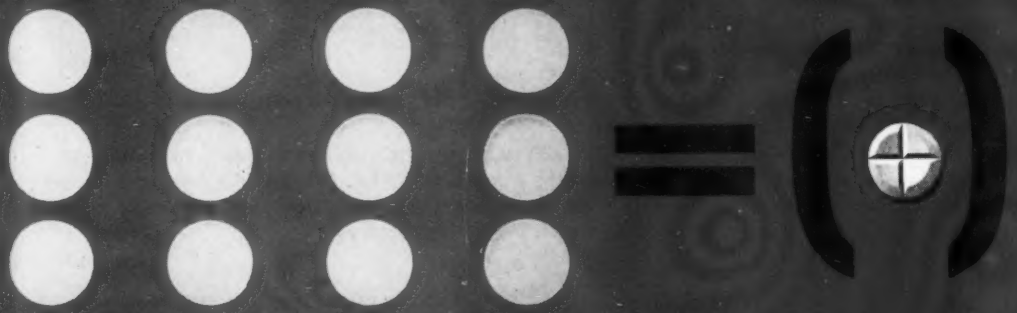

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• KREBIOZEN® AND CANCER

Q. I have a patient with metastatic carcinoma of the rectum (removed five years ago) whose family has asked me to treat him with Krebiozen. Does this drug have any value in the treatment of cancer?

M.D.—Pennsylvania

A. According to a report published in 1956 by Drs. A. C. Ivy, John F. Pick and W. F. P. Phillips, Krebiozen was developed by Dr. Stevan Durovic on a hypothesis that the reticuloendothelial system could be caused to secrete an anticancerous substance or a growth-regulating hormone into the blood stream in larger amounts than normal, and that such a hormone could be extracted from the blood stream by an organic solvent. The concept is based on the view that the body of a patient with cancer produces substances that can cause regression or prolonged arrest of the manifestations of cancer. Briefly, a culture of *Actinomyces bovis* cytolyzed with bovine bile salts is filtered through a Berkefeld filter and injected intravenously into horses. After four to six weeks, blood is taken from the horses; the serum is extracted with the organic solvent which is evaporated under vacuum; the residue is extracted with redistilled water, and the clear solution thus obtained is evaporated so that a whitish, slightly cream-colored powder remains. This powder is Krebiozen.

The vast majority of scientific evidence thus far available has failed to convince leading authorities in the field of cancer that this method of treatment has any real merit in arresting cancer or in curing it. The American Medical Association makes available a reprint of an article published in 1951 as a report of the Council on Pharmacy and Chemistry, which is supplemented by a statement in December 1957 that nothing has occurred since the first report was published which would cause modification of the view that Krebiozen is a secret drug without established merit in the treatment of cancer.

• DERMATITIS EXFOLIATIVA

Q. A two month old baby boy has suspected generalized dermatitis exfoliativa. The condition started as intertrigo over the neck, followed by intertrigo of the axillae and inguinal regions, and a week later by small subdermal pyoderma over the lower extremities on the lateral side. This later became generalized over the body. There was no pain, pruritus or fever.

ILOTYCIN® drops were then administered orally. The skin dried up and exfoliation followed, which resulted in continuous generalized scaling. To avoid sensitivity reaction to the mother's milk, SOBEE® milk was given, but, because diarrhea occurred, it was stopped after one can had been used. The baby is now on mixed feeding, including evaporated milk. He has also received VI-PENTA® drops, vitamin B_{12}, 50 μg. daily, and calcium gluconate powder. FISSAN® powder and paste have been applied locally. With this treatment the lower part of the right thigh is now clear of scales.

The parents both have asthma and allergic tendencies. Their other child, a three year old girl, has no symptoms of allergy.

What do you suggest in regard to diagnosis and treatment of this case?

M.D.—Philippines

A. There are many causes of dermatitis exfoliativa and a correct diagnosis necessitates a personal examination of the patient. Severe seborrheic dermatitis must be considered, which has nothing to do with the diet. Leiner's disease, a desquamative erythroderma of infants, is thought usually to be a staphylococcic infection and should be treated with antibiotics and B complex. Ritter's disease is also dermatitis exfoliativa.

Dr. Crotty reported four cases in the *A.M.A. Archives of Dermatology and Syphilology* (71: 587, 1955) of protracted diarrhea and secondary anemia, which were responsive to antibiotics and blood transfusions.

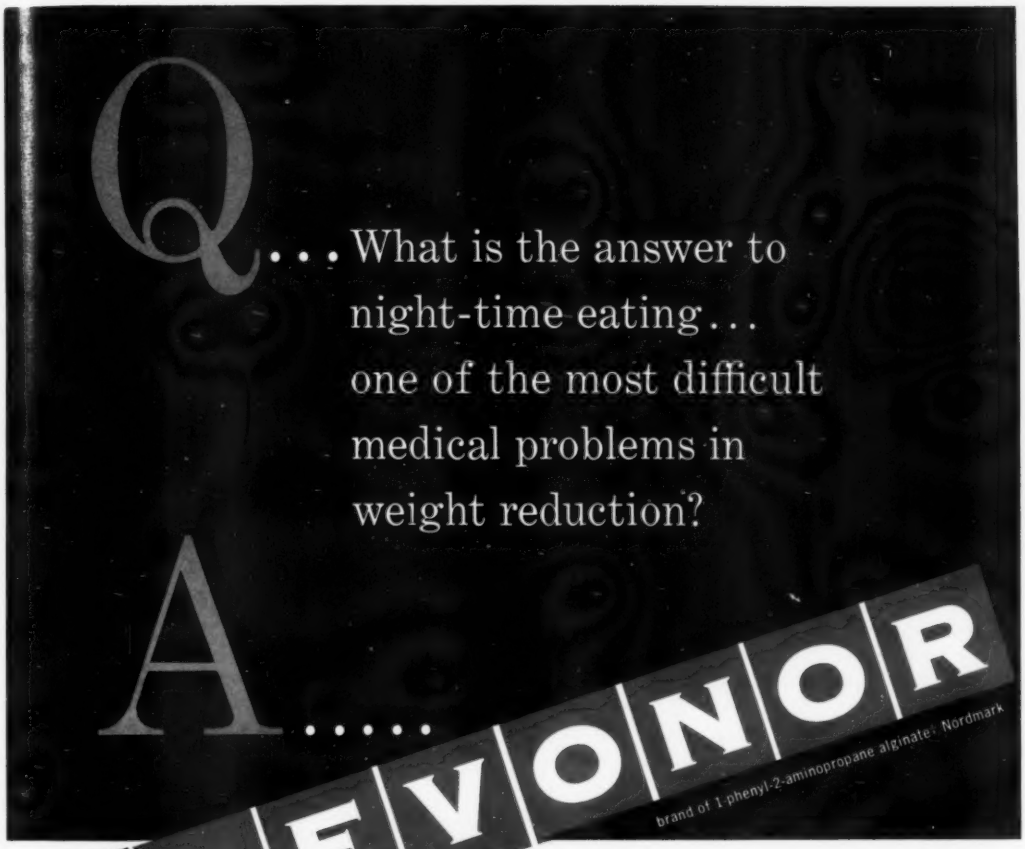
• PLASTIC SURGERY FOR DOUBLE EAR LOBE

Q. A child requires a plastic operation for a double ear lobe. What is the best age for performing this operation? Are the results cosmetically satisfactory?

M.D.—New York

A. This operation may be done anytime after an infant has gained sufficient strength, preferably after a child is a year old, but before he is affected by the remarks of other children. The procedure may be technically quite difficult and may require more than one operation. In this type of lesion where there is an excess of tissue, excellent results can be expected.

(Continued on page A-28)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• INFRA-ORBITAL PIGMENTATION

Q. A patient has persistent, abnormal infra-orbital pigmentation of gradual onset which is bilateral, brownish in color, restricted to the lower lids, does not wax and wane or have xanthelasmic plaques. At present this patient is hospitalized because of extremely slow recovery from a flulike intestinal upset with marked fatigability, and has had an unexplained high temperature twice since apparent recovery. I should appreciate any information on this subject.

M.D.—Iowa

A. Pigmentation of the skin of the lids, especially the lower lids, may be due to one of three things: (1) the ordinary dark rings around the eyes, which are due to dilatation of the venules occurring with fatigue, menstruation and debilitating diseases (and probably partly caused by loose areolar tissue and, in some cases, atrophy of the skin); (2) the so-called condition of melanoderma, which includes excess deposition of melanin pigment such as in the areola of the nipple and axillae, sunlight after tar sensitization, pregnancy, Addison's disease, bronze diabetes, Recklinghausen's disease and xeroderma pigmentosum; and (3) chronic exposure to or ingestion of metals such as silver, mercury and arsenic.

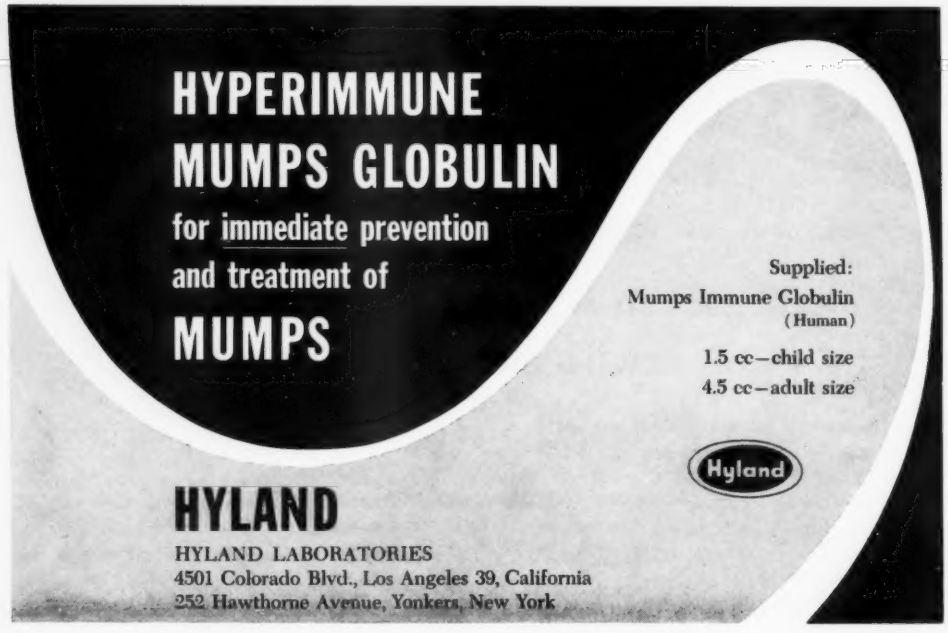
• READER COMMENTS ON APHTHOUS STOMATITIS

To The Editor:

The question with respect to aphthous stomatitis, which appeared in the January issue of Postgraduate Medicine, interests me. Several members of my own family have been subject to periodic ulcerative stomatitis for several years, usually provoked by consumption of walnuts.

About six months ago, after we began the daily use of a lemon bioflavonoid-ascorbic acid combination, it was noted that we could then eat walnuts without ulcer occurrence. We then increased our consumption of walnuts without ulcer occurrence with the exception of one occasion when we had been without the medication for a week. This ulcer promptly cleared up after we resumed the use of the bioflavonoid-ascorbic acid and we have had no recurrence since that time.

TRACEY G. CALL, PH.D.
Corona, California



What's happening in Medicine

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

DRUGS DOCTORS WOULD LIKE TO HAVE

Central section, American Pharmaceutical Association:

- Physicians need pharmaceuticals to use in treating obsessive compulsive neurosis, agents which induce peripheral vasodilation to increase cerebral circulation, an effective means of treating mental deficiency, agents that may be substituted for psychotherapy in treatment of impotence, psychic energizers that can reduce the need for sleep without evidence of undesirable side effects, and agents that would facilitate recall of stored memories.—Dr. Nathan S. Kline, Rockland State Hospital, Orangeburg, N.Y.
- Recent developments in treatment of nervous and mental diseases have triggered renewed interest in accurate measurement of drug effects. One of the more obvious basic needs is the development of stable and reproducible base lines against which to assess drug-correlated changes.—Joseph V. Brady, Ph.D., department of psychology, Walter Reed Research Institute, Washington, D.C.

ARTIFICIAL MUSCLE MOVES FINGERS

New York Academy of Sciences:

- An estimated 50,000 persons can be benefited by the discovery of a "hand motivator" that employs an artificial muscle to control grasping and to release movement of the thumb and first two fingers in the polio-paralyzed hand. The nylon fiber muscle, woven in a special geometric pattern, encloses a length of rubber tubing. A switch-controlled flow of compressed carbon dioxide gas fills the tube and causes the nylon to contract. Emptying of the tube relaxes the grip. The muscle transfers energy to the thumb and fingers with normal hand-grip intensity. Size of the muscle determines its contractibility; gas pressure, regulated by the valve, determines the strength.—Dr. Kenneth S. Landauer, National Foundation for Infantile Paralysis.
- Skin transplanted from embryo rabbits grew in 45 per cent of normal, untreated adult rabbits. The embryonic skin, obtained in the first trimester of gestation, was characterized by lack of formed connective tissue elements and of fibroblasts. Based on these results, human embryonic skin grafts were tried in eight patients. Four have maintained them, two for one year. The grafted skin, taken from embryos of less than four and one-half months' gestation, were almost transparent. Blood vessels were easily visible. Three of four subjects who held grafts were cancer patients. Thus their immunologic responses were probably less than normal.—Drs. Helene W. Toolan and Reuven K. Snyderman, Sloan-Kettering Institute and Memorial Center, New York.

COMPUTER IDENTIFIES EEG PATTERN

Second annual meeting of the Biophysical Society:

- An electronic computer has been used to identify 20 subjects on the basis of their EEG patterns. Although it has long been recognized that each person has his own brain wave signature, judgment has had to depend on the skill of experienced technicians. The computer will be used to study physiologic effects of drugs, fatigue and other factors affecting brain functioning.—B. G. Farley, Lincoln Laboratory, Massachusetts Institute of Technology, Cambridge.
- An analysis of the arterial system may be made by electronic means. An electric signal derived from catheterization of the aorta is fed into an analogue computer which is primed with equations that permit computation of the ratio of mass to elasticity, the elastic coefficient, and the coefficient of viscous drag. The technic may have value as a long-range predictor in cardiovascular disease.—Ralph W. Stacy, Ph.D., Ohio State University School of Medicine, Columbus.

PITFALLS OF NARCOTIC ADDICTION

Fifty-fourth annual Congress on Medical Education and Licensure:

- Medical curriculums should be revised to allow more time to teach students the pitfalls of having a narcotics license. Narcotic addiction among physicians is 30 times that of the general public. Of the 3000 addicts admitted yearly to the U.S. Public Health Institute at Lexington, Ky., 50 are physicians.—Dr. C. J. Glaspel, secretary, North Dakota Board of Medical Examiners.
- Because of the tremendous growth in medical knowledge, better means must be devised for the practicing physician's postgraduate education. The medical student must accept greater responsibility for his own education. His teachers can only give him a map and point the way.—Dr. Hugh H. Hussey, Georgetown University School of Medicine, Washington, D.C.
- The present approach to psychiatry as one specialty among many others which may not be entered without full training in general medicine makes it impossible to increase rapidly the number of psychiatrists. One way to meet the demand would be to train "psychologic physicians" who would concentrate mainly on psychologic and emotional problems, while "somatic physicians" would continue to handle physical ailments.—Talcott Parsons, Ph.D., Yale University, New Haven.

TRAINED "MIDWIFE" FOR OBSTETRICIAN

Illinois Congress on Maternal and Infant Care:

- There is need for especially trained obstetric nurses who would be competent to follow patients through labor, evaluate progress, immediately recognize danger signals, and, during emergencies, scrub and assist in delivery. Such nurses would be available to assist obstetricians in their offices and also to make house calls.—Dr. C. Lee Buxton, Yale University School of Medicine, New Haven.

CHEMOTHERAPY OF CHORIOCARCINOMA

National Crusade Meeting, American Cancer Society:

- A folic acid antagonist known as methotrexate has been used over a two year period in treating 16 women with far-advanced choriocarcinoma. Six have remained completely free of evidence of disease as manifested by hormone tests, x-rays and physical examinations. Five have some recurrence, three have shown a decisive initial response to therapy and are continuing under treatment, and two have died.—Dr. Roy Hertz, Endocrinology Branch, National Cancer Institute, Bethesda.

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MY DAD— HE HURT HIS BACK REAL BAD

"It happened at work while he was putting oil in something"

"He told Mom his shoulder felt like it was on fire"

"He couldn't swing a bat without hurting"

"But Doctor gave him some nice pills--and the pain went away fast"

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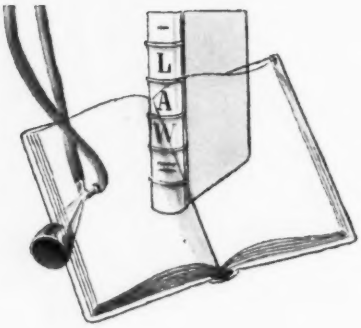

Forensic Medicine

The Management of Acute Chest Injuries

RUDOLF J. NOER*

University of Louisville School of Medicine, Louisville

CHEST injuries are increasing as the shocking number of highway casualties grows day by day in all areas of the nation, from the smallest hamlet to the greatest metropolitan center. The urgency of treatment is such that all surgeons, yes, even all physicians, whatever their field of activity and whatever their specialty, must be prepared to handle intelligently the problems which are peculiar to traumatic injury.

RUDOLF J. NOER

Patients with thoracic injuries are subject to the hazards common to injuries anywhere in the body, such as shock, hemorrhage and infection, but the urgent and unremitting need for constant respiratory function makes special demands on the physician. One cannot expect always to have available the surgeon whose particular interest in thoracic surgery makes him best able to treat these patients; the ubiquitousness of the automobile and the havoc that its thoughtless use may entail require of all an understanding of the basic principles involved in treating the injured patient, whatever the region of the body involved.

For convenience of discussion, one may subdivide the problem of acute chest injuries into four categories: (1) those relating to the thoracic cage and its functions, (2) those in which the entry of air and fluid disturbs pleural function, (3) injuries of the lung itself, and (4) disturbances in the patency of the tracheobronchial tree. Wounds of the diaphragm and injury of the esophagus, heart and great vessels, serious though they may be, cannot be discussed in this brief presentation, and I shall confine my remarks primarily to a consideration of injuries that directly jeopardize respiratory function.

Injuries to the thoracic cage are extremely common. Rib fractures, however painful, are serious only when they are multiple or when the broken ribs injure other structures. Strapping, once an almost universally accepted practice, is

(Continued on page A-42)

*Department of Surgery, University of Louisville School of Medicine, Louisville, Kentucky.

Reprinted, with modifications, from the *Chicago Medical Society Bulletin*, issue of January 5, 1957.

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why ATARAX? *For ataractic effect:* One of the most effective—and probably the safest—of tranquilizers, ATARAX frees the angina patient of his constant tension and anxiety. Ideal for the on-the-job patient. And ATARAX has a unique advantage in cardiac therapy: it is anti-arrhythmic and non-hypotensive.

why combine the two? *For greater therapeutic success:* In clinical trials, CARTRAX was demonstrably superior to previous therapy, including PETN alone. Specifically, 87% of angina patients did better. They were shown to suffer fewer attacks . . . require less nitroglycerin . . . have increased tolerance to physical effort . . . and be freed of cardiac fixation.

1. Russek, H. I.: Postgrad. Med. *19*:562 (June) 1956.

Dosage and Supplied: Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. ATARAX) 3 to 4 times daily. When indicated this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. ATARAX.) For convenience, write "CARTRAX 10" or "CARTRAX 20." In bottles of 100.

CARTRAX should be taken 30 to 60 minutes *before* meals, on a continuous dosage schedule. Use PETN preparations with caution in glaucoma.

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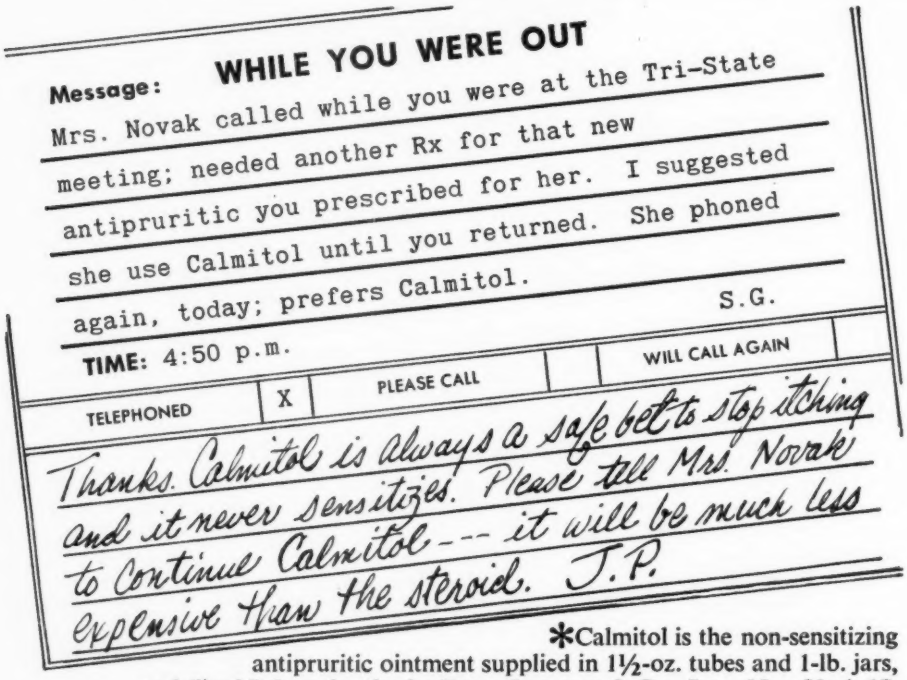
now considered inadvisable except for the occasional fracture of one or two ribs without other injury. The limitation of respiratory activity produced by strapping, while it reduces pain, at the same time interferes with both aeration and adequate elimination of tracheobronchial secretions. Experience with thoracic wounds during World War II demonstrated clearly the deleterious consequences of the "wet lung."

Intercostal nerve block is far and away the most important consideration in the management of multiple rib fractures. It is best accomplished paravertebrally at the angle of the rib where the nerve lies in a good position for injection and where the artery is shielded by the rib and so is unlikely to be injured. A needle is introduced until it makes contact with the rib, and then it is withdrawn slightly and introduced just below the lower margin of the rib, at which point 5 cc. of 1 per cent procaine is infiltrated. This procedure should be carried out for each of the two intercostal nerves above and below each fractured rib. The increased respiratory activity that results will do more than anything else to facilitate maintenance of respiratory function and prevent retention of secretions.

Multiple fractures of several ribs may produce the so-called stove-in chest syndrome in which there is a free to-and-fro paradoxical motion of the involved portion of the thoracic cage, with shifting of the mediastinum and resultant inefficient respiratory function (figure 1). This "paradoxical respiration" constitutes one of the most critical problems in thoracic trauma; if such injury is extensive, death will ensue unless the patient receives prompt and proper treatment.

If the paradoxical action is minimal, one may stabilize the thoracic cage by placing a light sandbag over the area involved. If this simple assistance does not handle the problem, however, one is well advised to support the floating portion of the chest wall by traction applied to the rib fragments. Various devices have been proposed and it matters little which one is chosen, just so the desired results are obtained. Perhaps the simplest is the application of towel clips or tenacula to the broken rib fragments with weights connected across pulleys to the handles of these instruments (figure 2). A bit of experimenting will reveal the amount of weight that will just stabilize the injured portion of the chest without unduly pulling on the rib fragments; usually not more than 2 to 5 lb. of weight is required. Con-

(Continued on page A-44)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*Calmitol is the non-sensitizing antipruritic ointment supplied in 1½-oz. tubes and 1-lb. jars, and (liquid) 2-oz. bottles by THOS. LEEMING & CO., INC., New York 17.

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1. Wright, W. T. Jr.; Pokorny, C., and Foster, T. L.: J. Kansas M. Soc. **57**:410, 1956.
2. Terman, L. A.: Illinois M.J. **3**:67, 1957.
3. Moyer, J. H.; Dennis, E., and Ford, R.: Arch. Int. Med. **96**:530, 1955.

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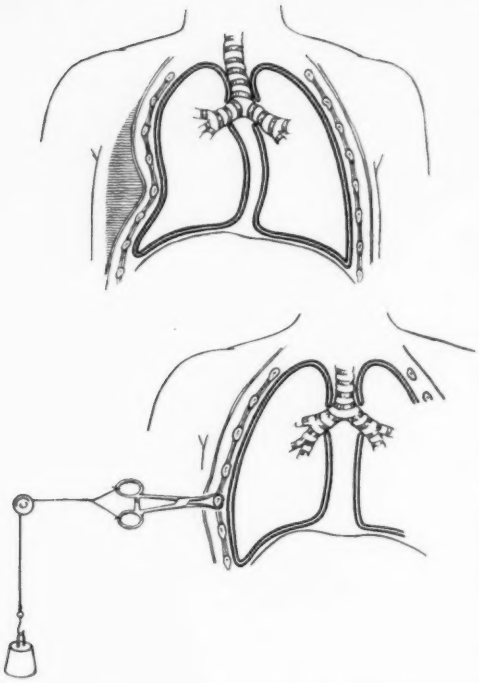

FIGURE 1 *(top)*. "Stove-in chest" with resultant paradoxical motion of the thoracic wall.

FIGURE 2 *(bottom)*. Stabilization of thoracic wall by a towel clip applied with traction to one or more of the broken ribs. The weight applied should be just sufficient to prevent paradoxical motion.

stant attention to this setup is required and the weight may need adjustment from time to time. Ordinarily this method of stabilization need not be continued for more than two or three days. To determine when it can be discontinued, one can remove the weight temporarily; if the patient does not respond well, one can restore just enough weight to return respiratory activity to normal. It is not often that one is forced to use this type of support to the chest wall, but it is all-important to institute it without delay when necessary.

Pleural function is commonly disturbed by the introduction of air or blood into the pleural cavity. Infection often complicates the situation, producing a third category of pleural involvement, pyothorax or empyema. These three problems, pneumothorax, hemothorax and pyothorax, together with the entity referred to as "organizing hemothorax," comprise the greatest part of our problems in thoracic trauma (figure 3).

Pneumothorax may be either open or closed. Closed pneumothorax is said to exist when there is no communication between the pleural cavity and the external air (figure 3A). Open pneumothorax results when the wound in the chest wall does not close and air continues to go in and out. This is known as a sucking wound. Figure 4A and B depict open pneumothorax under contrasting situations. The degree of respiratory disturbance produced by an open pneumothorax relates directly to the size of the communication between the chest wall and the exterior. So long as the opening is smaller than the trachea, though a pneumothorax is produced, the competition for flow of air remains in favor of that taking place through the tracheobronchial tree. When the opening in the chest wall is larger than the trachea, respiratory activity takes in air more easily through the chest wall than through the trachea. The resultant gross disturbance of respiratory function obviously is greatly disadvantageous to the patient and death will ensue unless something is done promptly to close the opening in the chest wall. One should close the opening with whatever

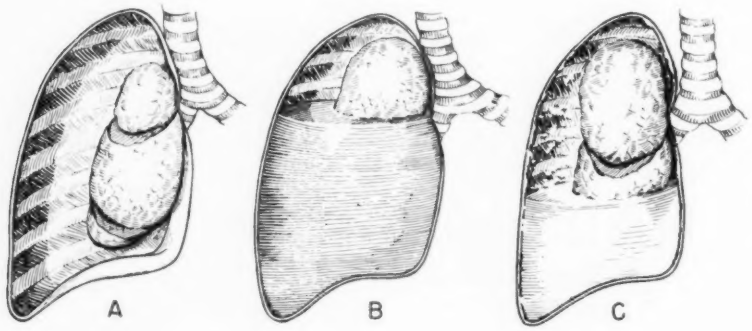

FIGURE 3A. Pneumothorax. B. Hemothorax. C. Empyema. Note deviation of trachea in the first two, and not in empyema, where the continued inflammatory process produces relative fixation of mediastinum.

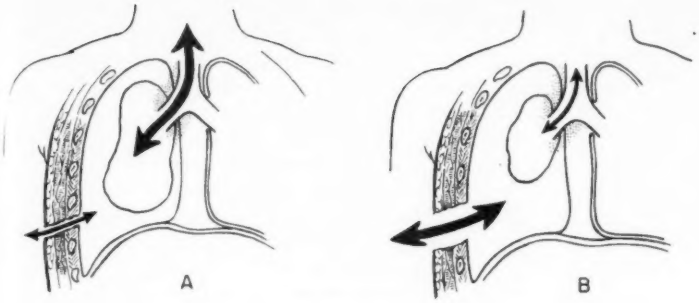

FIGURE 4. Open pneumothorax. A. An opening smaller than the trachea produces relatively little respiratory interference. B. An opening larger than the trachea produces gross disturbance of respiratory function.

means is available; the palm of one's hand will suffice until a more permanent occlusive dressing can be applied to the defect.

Closed pneumothorax is most often seen in association with hemothorax—hemopneumothorax (figure 3B). Presence of air and blood in the pleural cavity inevitably produces at least partial collapse of the lung and usually interferes considerably with respiratory function. It is most important to treat these patients promptly by removing as much air and fluid as possible from the chest at the earliest possible time. It was once thought that aspirated blood should be replaced by air, but we now know that this is not only undesirable but also harmful. The sooner complete re-expansion of the lung can be obtained by aspiration of fluid and air, the greater will be the likelihood of prevention of further complications.

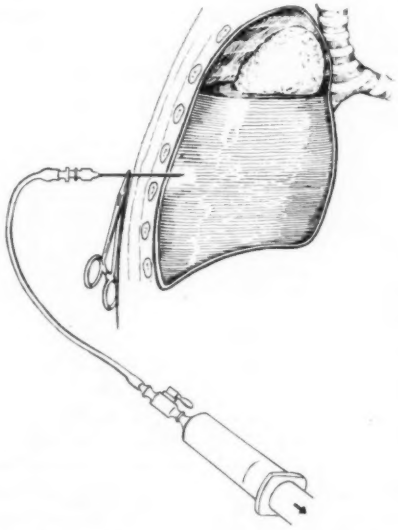

FIGURE 5. Aspiration of air and fluid from the pleural cavity. Note hemostat in place to minimize motion of the needle during aspiration, and two way stopcock attached to syringe.

Aspiration is best carried out intercostally in the lower part of the chest at about the sixth or seventh interspace (figure 5). Never allow the tube connected to the aspirating needle to have free communication with the atmospheric air, lest additional air be permitted to enter the chest. A two way stopcock applied at the end of the syringe provides a simple and effective means of preventing such re-entry of air into the pleural cavity while the blood is emptied from the syringe. To avoid injury to the underlying lung by the aspirating needle, a hemostat may be applied to the needle at the point where it enters the skin to keep it in the same relative position it occupied when air or blood was obtained; this will prevent advancing the needle too deeply during aspiration and also minimize motion of the needle tip, which might tear the expanding lung.

It may be necessary to aspirate air and blood two or three times a day for the first two or three days, and one should aspirate as often as required to maintain re-expansion of the lung. This is best checked by a combination of physical examination and x-ray examination. If several needle aspirations fail to maintain re-expansion of the lung and thus obliterate the pleural space created by the trauma, it is better to insert a catheter for so-called closed drainage. Under local anesthesia, a trocar is passed into the chest wall and a catheter (No. 18 French or thereabouts) is passed through it and connected to a water-seal bottle. If there is blood in the pleural cavity, the sixth or seventh interspace in the posterior axillary line is the desirable location for the tube. To aspirate air only, the catheter is

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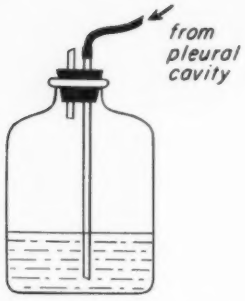

FIGURE 6. Water-seal bottle for use with catheter drainage of the pleural space by patient's own respiratory activity.

probably a bit more effective in the second interspace in the midclavicular line anteriorly. Sometimes it is necessary to insert two tubes in order to maintain complete collapse of the pleural cavity and in this way obtain complete expansion of the lung.

It is important to place a clamp on the catheter while it is being passed through the trocar, to prevent entry of more air into the chest. The catheter is then connected with a water-seal drainage bottle (figure 6). The tube is led out of the chest wall and into a bottle by connecting with a glass tube whose tip lies about ½ to ¾ in. below the surface of the water in the bottle. As the patient inspires, he expels the air and blood from the pleural cavity, and the weight of the water going back up the tube during expiration prevents further aspiration of air into the pleura. Some physicians apply suction to this bottle, and others feel that any opening in the lung is apt to close more quickly with a simple water-seal drainage bottle. For positive catheter aspiration, water siphon or a motor suction apparatus is used. It is then important to regulate the degree of suction. For this purpose a second bottle is added with a glass tube that projects down beneath the surface of the water so that its depth controls the degree of suction (figure 7). Application of too powerful suction may result in the catheter clinging to the lung or the chest wall and thereby becoming partially occluded. With motor suction it is desirable to add a third bottle to protect the motor from damage in case of overflow (figure 8).

Pyothorax or empyema (figure 3C) is a late complication commonly associated with the organization and clotting of blood in the pleural cavity. Infection of simple pleural effusion is uncommon, but the association of infection with blood clotting in the pleural cavity is an extremely common sequela of hemothorax that has not been adequately treated by aspiration. With or without infection, organization of blood within the pleural cavity will inevitably result in deposition of a firm, unyielding layer on the surface of the partially collapsed lung. If allowed to go on to complete organization, permanent loss of pulmonary function will result. Should this situation occur, it is important to perform the operative procedure known as decortication, consisting chiefly of opening the chest and removing from the surface of the lung the organized layer of blood so that the lung can once again expand to fill the pleural cavity.

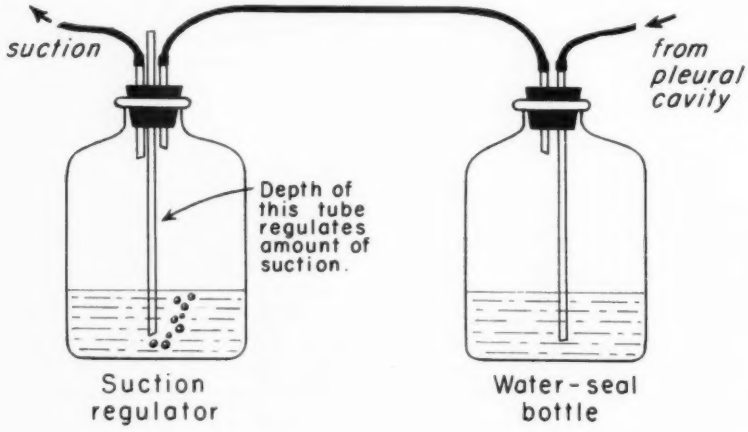

FIGURE 7. Two bottle suction set; the second bottle is for control of the degree of suction.

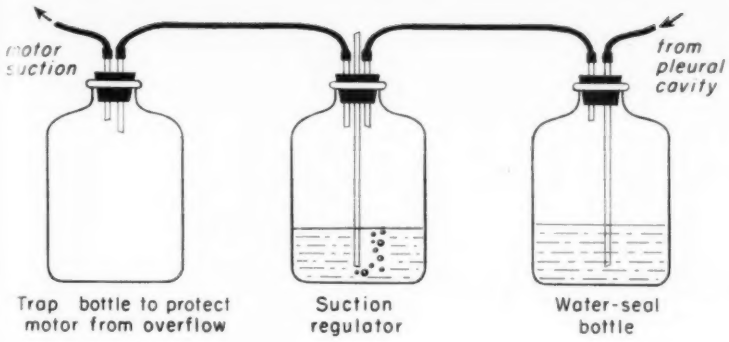

FIGURE 8. Three bottle suction set; the third bottle is added to protect against motor damage in case of overflow.

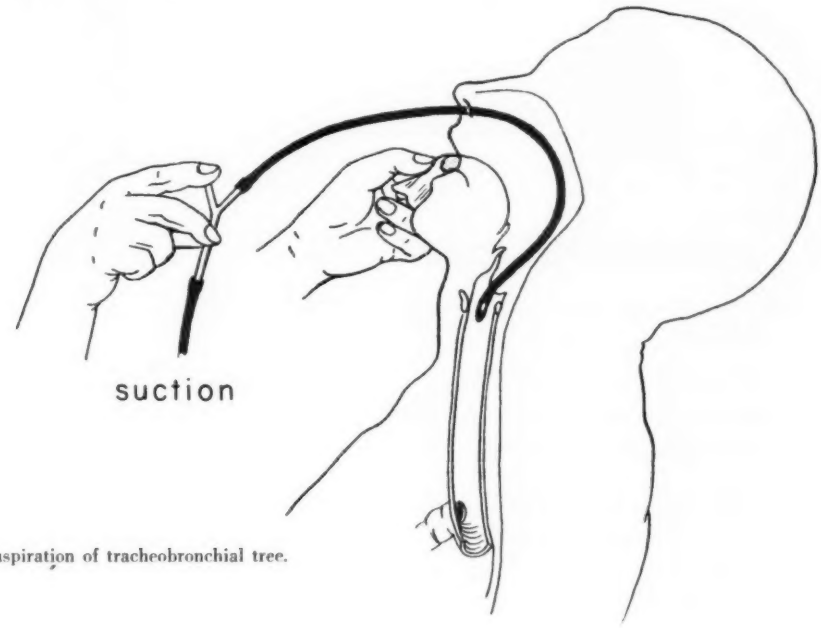

FIGURE 9. Catheter aspiration of tracheobronchial tree.

We must never forget the importance of maintaining a free and unobstructed tracheobronchial airway. Simple catheter aspiration is the easiest and most readily available means for removing retained secretions (figure 9). With the patient's head in slight hyperextension produced by a small pillow or folded towels under the shoulders, a catheter can be passed through the nose down to the larynx, and as the patient inspires it can be pushed on into the trachea. Turning the patient's head to one side or the other as the catheter is advanced will cause it to pass into one or the other main bronchus. A Y tube enables one to apply suction intermittently so that there will not be too much at any one time and so that respiratory exchange can be maintained. If this procedure is not effective, bronchoscopy may be required for more adequate removal of secretions.

One of the most important considerations is tracheotomy, or, more properly, tracheostomy, the establishment of a functioning communication with the external air at the neck. In instances of severe thoracic trauma, tracheostomy should be considered far more often than it is. The operation is easily carried out under local anesthesia, it is without great hazard, and it

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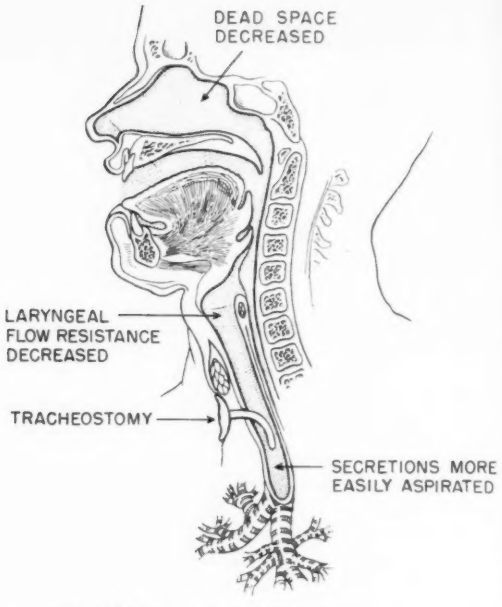

FIGURE 10. Advantages of tracheostomy.

(From RANSDELL, H. T., JR., Am. Surgeon 22:258, 1956. Reproduced courtesy of The Williams & Wilkins Company.)

offers many advantages to the patient with severe thoracic injury. Secretions are much more easily aspirated through the tube. The resistance of air flow and the amount of dead space in the upper respiratory passages being considerable, the patient will immediately breathe more easily if these areas are bypassed by the performance of tracheostomy (figure 10). I think we can say, as a rule, that all patients with severe respiratory difficulty from whatever cause would benefit by having a tracheostomy, for the reasons listed.

In summary, the patient with thoracic trauma shares the hazards common to trauma in all areas of the body. He has imperative needs related to the necessity for maintaining respiratory function. Adequate breathing can be obtained by treating rib fractures properly, by keeping pleural function active through the removal of accumulated air or blood, and by insuring an unobstructed tracheobronchial tree through aspiration of secretions and, whenever necessary, tracheostomy. Only by attention to all these various elements of respiratory function will we be able to restore the patient's normal breathing. Only as we maintain this activity will we be able to assure survival and recovery of the patient with severe thoracic injury.

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*Jackson, A. S.: Journal-Lancet 76:45 (Feb.) 1956.

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*Steinberg, M. H.: Angiology 6:519 (Dec.) 1955.

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Veins fill rapidly from below	Filling not accentuated	Valves of communicating veins are incompetent	Injection
Veins fill slowly from below	Rapid filling from above	Saphenofemoral valve and valves of superficial veins are incompetent	Operation
Veins fill rapidly from below	Filling accentuated from above	Incompetence of all valves	Operation

Hyman, H. T.: An Integrated Practice of Medicine, Philadelphia, W. B. Saunders Company, vol. 4, 1947, p. 3941.

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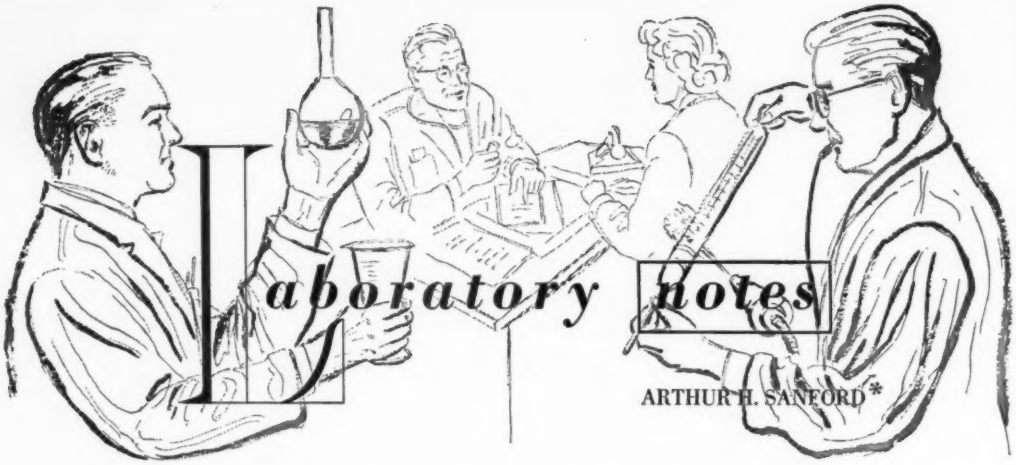


Laboratory notes

ARTHUR H. SANFORD*

Equipment for a Small Office Laboratory

I HAVE been asked from time to time what materials and supplies are necessary to equip a small laboratory. Lippman[1] has answered this question very well. I am publishing here the advice found on pages 111 and 112 of his monograph.

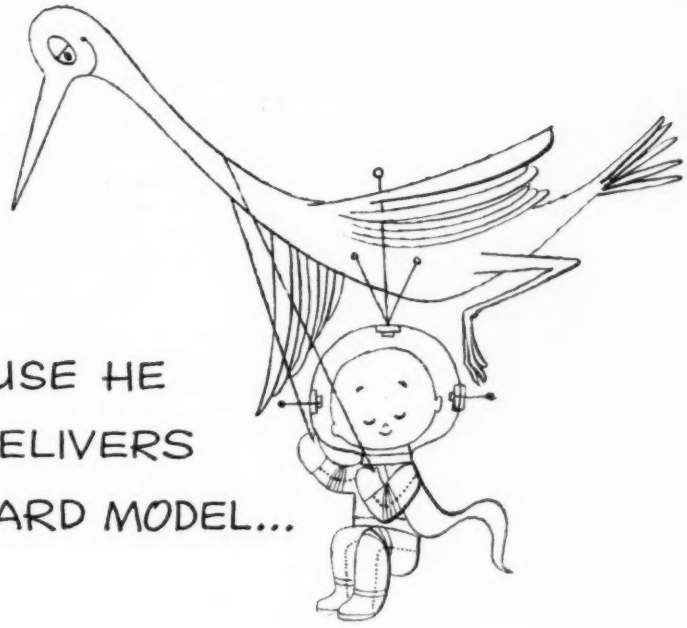
"Equipment and Materials for Basic Technic

It is the purpose of this list to aid the physician who is establishing an office in selecting the equipment and materials necessary to perform all the basic technics described. Where material brand names are specified, it is because the brands named offer notably greater convenience, durability or economy than other comparable equipment. Quantities recommended are minimal, planned to equip an office handling not more than six urine examinations per day. Quantities of chemicals recommended consider convenience, amount used and price reductions for bulk purchase, where possible. All chemicals used should be of 'reagent grade' and all stains should be 'certified' quality.

Beaker, PYREX®, 250 ml.—6.
Bottles, reagent, glass-stoppered, 500 ml., 1000 ml., 3 each; 125 ml., 250 ml., 6 each.
Burner, Bunsen, with fishtail, tripod and wire gauze.
Buret, delivery, 25 ml.—1.
Centrifuge, clinical, conical head, with induction motor (Precision Scientific Co., Chicago, Cat. No. 67377).
Containers, conical, quart-size, paraffined, paper, type used for milk (obtainable from wholesale dealers in paper containers).
Cylinder, graduated, Pyrex, 25 ml., 100 ml., 500 ml., 1000 ml., 2000 ml., 1 each.
Flask, Erlenmeyer, Pyrex, 5 ml., 125 ml., 6 each.
Flask, volumetric, Pyrex, 500 ml., 1000 ml., 1 each.
Hemacytometer.
Lamp, substage microscope.
Microscope, clinical.
Pipet, rubber bulb dropping, drawn from 8.00 mm. (o.d.) Pyrex tubing (5 lb.).
Pipet, serologic, 5 ml.—3.
Pipet, volumetric, delivery, 0.5 ml.—6.
Rack, test tube, holes for centrifuge tubes, 12 holes in a row, 3 rows—2.
Stoppers, rubber and cork (rubber sizes 0, 00, 4, 5 are the most useful).
Support, ring-stand, with buret clamps.
Thermometer, chemical, centigrade, total immersion (for room temperature)—1.
Tube, Pyrex, no lip, 14 by 150 mm.—36.
Tube, graduated centrifuge, 15 ml., conical tip, Pyrex—12.
Tube, plain centrifuge, 15 ml., conical tip, Pyrex—12.
Tube, Shevky-Stafford, Pyrex—6 (obtainable from A. H. Thomas Co., Philadelphia).
Urinometer, Squibb.
Acid, acetic, glacial, 1 lb.
Acid, hydrochloric, concentrated, 1 lb.
Acid, nitric, concentrated, 1 lb.
Acid, phosphotungstic, ¼ lb.

(Continued on page A-68)

*Emeritus Staff, Section of Clinical Pathology, Mayo Clinic; Director of Laboratories, Rochester State Hospital, Rochester, Minnesota.



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Copper sulfate, crystals, ¼ lb.
Diphenylcarbazone (Eastman Kodak No. 4459), 10 gm.
Distilled water.
Mercuric nitrate, ¼ lb.
NITRAZINE® paper, 2 tubes.
Sodium carbonate, crystals, 1 lb. (*Anhydrous* sodium carbonate may be substituted, using one-half the specified quantity, in preparing Benedict's solution.)
Sodium chloride, ¼ lb.
Sodium (or potassium) citrate, 1 lb.
Sodium nitroprusside, 10 gm."

It is obvious that if some good method of determining hemoglobin and some stains were added, the equipment listed by Dr. Lippman would also suffice for making hematologic examinations. I would suggest that plastic bottles would be also useful, either in place of or in addition to the glass-stoppered bottles.

REFERENCE

1. LIPPMAN, R. W.: Urine and the Urinary Sediment. Ed. 2. Springfield, Illinois, Charles C Thomas, 1957.

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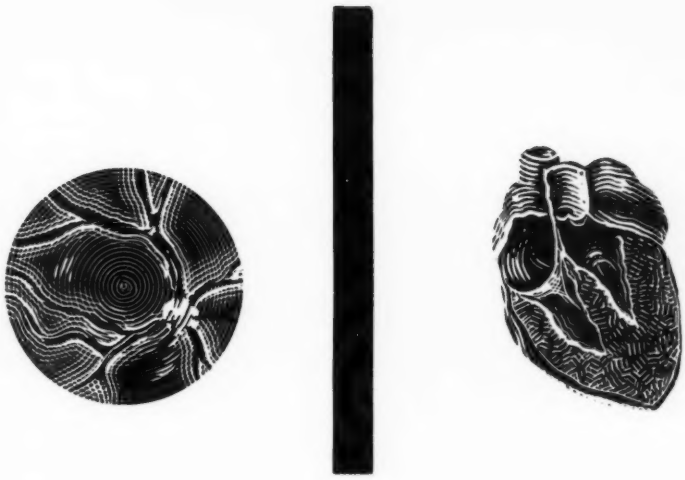

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* REFERENCE:
Crawley, C. J. *et al*: N. Y. State J. of Med. 55:*23* (Dec.1) 1955: pp. 3461-3463.

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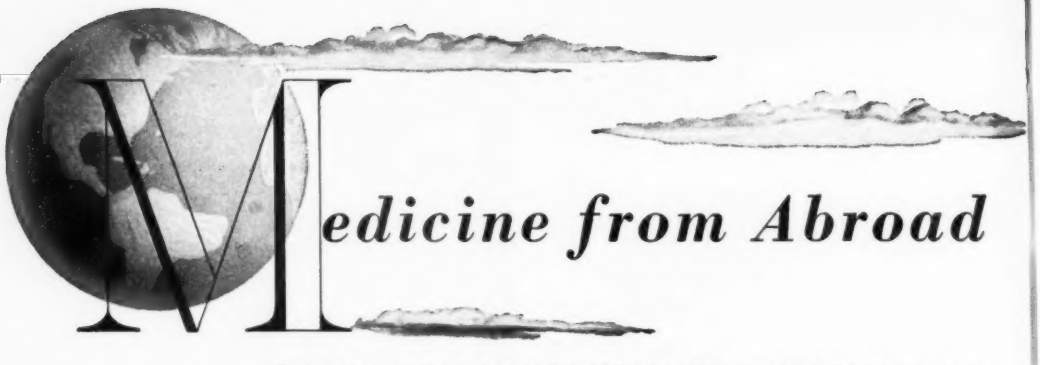

Medicine from Abroad

FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS

AUSTRALIA

Mortality rate in cardiac operations—In the Syme memorial lecture, "Surgery of the heart" (M. J. Australia 2:1, 1956), C. J. Officer Brown recorded the results of 616 cardiac operations that were done at the Alfred Hospital, Melbourne. The mortality rate was as follows: pericardial resection, 1 in 17; patent ductus arteriosus, 1 in 191; tetralogy of Fallot, etc., 22 in 190; coarctation, 5 in 63; pulmonary stenosis, 2 in 15; mitral stenosis, 6 in 122; aortic stenosis, 1 in 2; atrial septal defect, 3 in 6; vascular ring, none in 4; pulmonary aortic fenestration, 1 in 2; coronary sclerosis, none in 2; total anomalous pulmonary veins, 1 in 1; ectopia cordis, 1 in 1. These results show that the risk to life in cardiac operations compares favorably with that in other operations of the same magnitude.

Hiatal hernia—At a symposium on the problem of hiatal hernia held by the Victorian branch of the British Medical Association (M. J. Australia 2:126, 1956), Dr. W. E. King in discussing conservative management suggested that a bland diet is necessary only when esophagitis is active. In other cases, he advocated a normal diet, although the patient should avoid fried or highly seasoned foods. He also emphasized the importance of weight reduction and avoidance of tight corsets. Operation was advisable if persistent hemorrhage, severe dysphagia or stricture was present.

Dr. A. E. Piper spoke on the duty of the radiologist to demonstrate the type and size of the hernia and, most important of all, to demonstrate reflux. He believes that, when reflux is present, esophagitis in Australian patients is much lower than the 75 per cent claimed by Johnstone.

Dr. K. N. Morris discussed the surgical aspects of hiatal hernia. In 116 patients with this condition, he found there were 101 women and only 15 men, and 91 of the patients were more than 50 years old. The most common symptoms were dyspepsia (42 patients), pain (22 patients) and dysphagia (17 patients). Since 1951, the hernia has recurred in only 4 of 90 patients who have been operated on using Allison's transthoracic approach. He concluded that patients who have been miserable for years with chronic dyspepsia, pain and dysphagia as the result of a hiatal hernia are usually completely relieved by operation.

Cortisone and anesthesia—In an address to the Australian Society of Anesthetists (M. J. Australia 2:289, 1956), Dr. Patricia Wilson pointed out that cortisone has such a definite place in modern therapeutics that the surgeon and the anesthetist must be prepared to manage patients treated with this drug. There is considerable evidence that cortisone may cause adrenal atrophy which remains for some time after treatment has been discontinued. When there has been prolonged treatment or evidence of hypercortisonism at any stage, these patients should be treated prophylactically with cortisone before operation. All other patients who have been treated previously with cortisone should be managed with great care with regard to preoperative preparation, choice of anesthetic, degree of surgical trauma and postoperative supervision.

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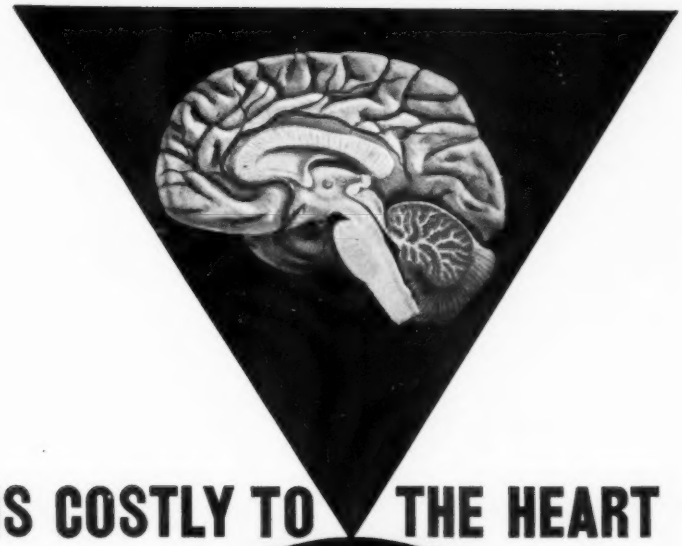

ANXIETY IS COSTLY TO THE HEART

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**Waldman, S. and Peiner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 9:1075, July 1957.*

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ENGLAND

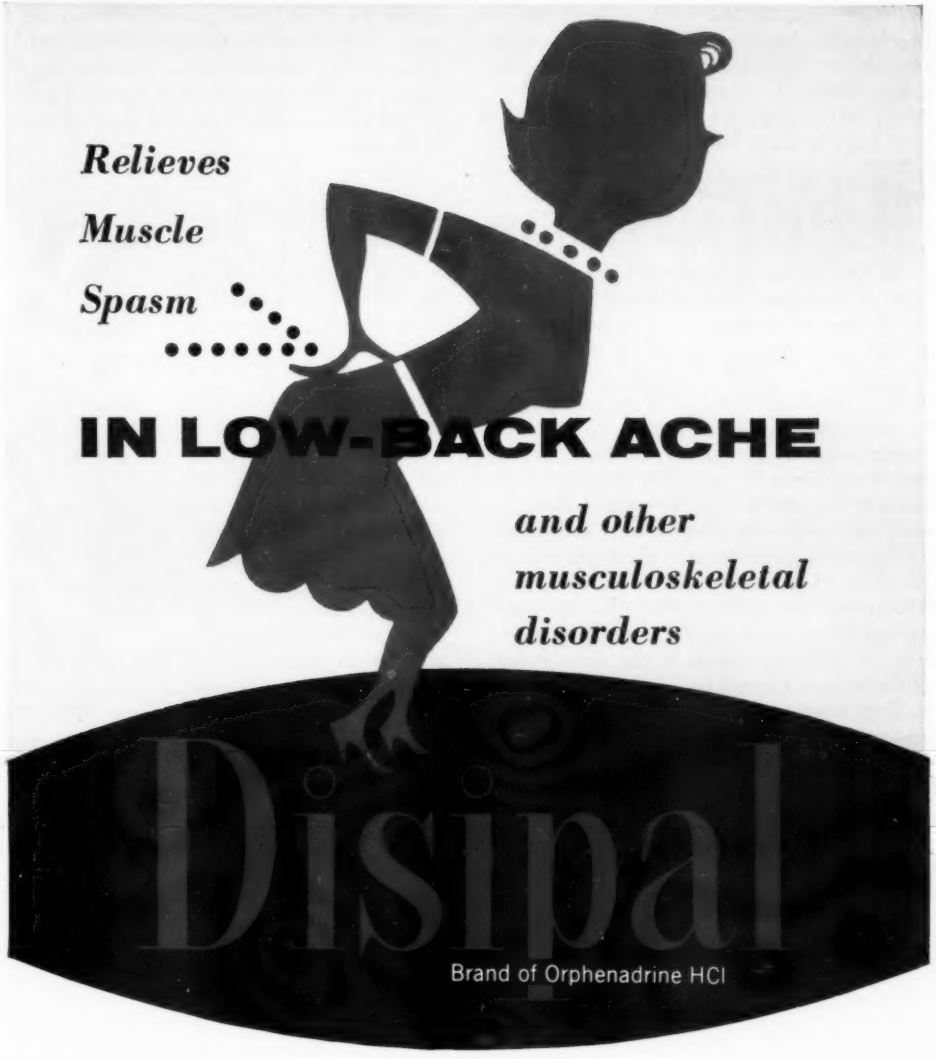
The physiology of memory—At a recent meeting of the Royal Society of Medicine, Dr. W. Ritchie Russell gave an interesting and stimulating address on this subject, in which there are still more unsolved than solved problems. The activity of the mature central nervous system usually falls into well-worn patterns which have formed during the years of development. These furrows of habit first become ruts which guide and then chains which control our responses to a greater or lesser degree. These bonds of habit affect very strongly the simple motor performances such as handwriting. This capacity to repeat a previous response is clearly an essential part of the physiology of memory. Another important aspect is the capacity of all forms of animal life to encourage or discourage a response according to whether it appears to be advantageous or disadvantageous to the organism. Ever since anatomists discovered that the central nervous system is built up of neurons, it has been realized that much must depend on the properties of these units and on the manner by which they form synaptic connections with each other. It is, therefore, of great importance that in recent years neurophysiologists have demonstrated that transmission from one cell to another is greatly augmented if there has been preceding activity across this connection.

The time factor is only one of many factors which are concerned with memory. For example, the factor of attention seems to be perhaps the most important of all, for afferent impulses pouring in from the special senses seem to be extinguished automatically, unless they arouse what Pavlov called the "What is it?" reaction. The gradual strengthening of a memory with the passage of time depends on its remaining relatively isolated and not becoming confused by a large number of very similar memories. If our memories are, in fact, facilitated neuronal circuits which never rest, how can we prevent them from constantly disturbing our lives? Thus, if the memory of how to swim involves circuits which never rest, why are we not constantly waving our arms and legs around in response to this constant activity? The answer would seem to lie in a study of what happens to nearly all impulses reaching the nervous system, for it is evident that only a minute fraction of, say, visual afferent impulses from the retina are "seen" at all. It seems that nearly all the afferent impulses to the central nervous system are immediately extinguished by an inhibitory process. Our memory neuronal patterns can remain constantly active without reaching what we call consciousness. What enables us to think of one of our memories or to remember something we have seen or heard seems to depend on some general alerting process.

Anticoagulants in myocardial infarction—The use of anticoagulants in the treatment of myocardial infarction has increased greatly in recent years, and practically all reports have acknowledged their value. The only serious argument has been whether these drugs should be used in so-called good-risk cases as opposed to bad-risk cases. Bad-risk patients have been defined as those with a history of previous infarction, who have intractable pain, extreme or persistent shock, significant cardiac enlargement, arrhythmia or diabetic acidosis. From 1951 to 1957, Dr. H. Toohey of New End Hospital, London, studied a series of 326 patients with myocardial infarction who were strictly classified according to all the bad-risk factors (Brit. M. J. 1:252 [February] 1958). The number of good-risk patients was 25.7 per cent, but the mortality rate was only 13.6 per cent, confirming the view that anticoagulants are of real value in the treatment of acute myocardial infarction. Dr. Toohey is of the opinion that bad-risk patients should be treated with anticoagulant therapy; but the control of anticoagulant therapy calls for adequate laboratory technic and administration of the drug by a physician experienced in its use. Vitamin K_1 is invaluable in the control of hemorrhage due to overdosage with anticoagulant drugs, but it must be used with caution and in very small doses as it is so potent. Certain drugs many enhance the effect of oral anticoagulants or may cause hemorrhage. As a result, the administration of oral antibiotics, particularly the broad-spectrum drugs such as the tetracyclines and, to a lesser extent, penicillin, may call for a reduction in the dose of the anticoagulant drug. Aspirin, phenylbutazone and, probably, quinine should not be given at the same time as anticoagulant therapy, and liquid paraffin is also best avoided.

Control of difficult epistaxis—One would

(Continued on page A-86)



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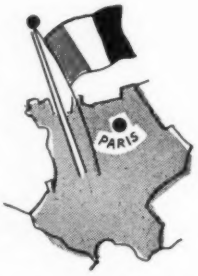
have thought that the last word on the treatment of nosebleeding had been said long ago, but Dr. John Roberts, a well-known Welsh otolaryngologist, has published (Practitioner 180:211 [February] 1958) a practical article on this subject written from a novel viewpoint. It is fortunate that, in the vast majority of cases, nosebleeding comes from an erosion of the wall of a small blood vessel on the front and lower part of the nasal septum, described as the "area of predilection" by the American surgeon Little in 1879. Because of the lesion's accessibility, the bleeding is easy to control, often even by finger pressure on the ala nasi. But there is also a small group of cases, seen more often in adults, in which the bleeding proves obstinate, copious and sometimes alarming. The familiar rules of treatment include placing the patient in a sitting posture, bathing his face and neck with ice-cold water, having him breathe through his mouth, and suppressing his swallowing which is apt to dislodge clots lying on the upper surface of the soft palate; an injection of morphine also is valuable. Dr. Roberts points out, however, that in some cases the eroded blood vessel lies in the vault or lateral wall of the inferior meatus of the nose underneath the posterior one-third of the inferior turbinal. This is where the descending palatine vessels emerge from the sphenomaxillary fissure and start to diverge over the lateral nasal wall. Whether they are venous or arterial is of no practical importance, but in this area they lie superficially and without much support under the mucosa, where they are prone to dilatation and rupture.

After the nose has been cleansed, the packs removed, and the blood clots lifted out with forceps or blown or sucked out, with the aid of a head lamp the whole nasal passage is cleansed, anesthetized and opened out for inspection. A search is made underneath the posterior half of the inferior turbinal, using a small, dry wool mop on a fine carrier. As a rule, it will be found that a repetition of this test will reveal a small but significant trickle of blood from this hidden spot. The application of the cautery point is not recommended when the bleeding area is out of sight. Instead, using a fine septal elevator, the posterior half of the inferior turbinal is gently infracted away from the outer nasal wall, and the corresponding part of the inferior meatus is filled with a paraffined 1 in. wide (2.5 cm.) ribbon gauze pack, the first 6 in. (15 cm.) of which has been medicated with compound tincture of benzoin. The turbinal is next replaced, and the remainder of the gauze is firmly packed between the back part of the septum and the inferior turbinal, which brings full pressure to bear on the bleeding point. The gauze pack is removed gently on the third or fourth day, and no further treatment is necessary.

FRANCE



New methods of induction—In a recent issue of *La Presse médicale*, Dr. Djourno of Paris tells of a new method of nerve stimulation in which he imbeds an electric apparatus in the mass of tissues close to the nerve which he finds suitable for stimulation. Since unchangeable substances, such as nonoxidizing metals insulated in plastic material, are perfectly well tolerated by the tissues, he inserts into the tissues a miniature apparatus consisting of a nucleus of high magnetic permeability around which a few thousand spiral turns of a well-insulated, extremely fine silver wire are wound to form an induction coil. The entire device is coated with plastic material from which the stainless steel ends of two wires protrude. After the wound is sealed by scar tissue, Dr. Djourno stimulates the indwelling apparatus from a distance by means of an induction coil through which an appropriate current passes. When placed on the external surface of the body, the primary coil sends through the tissues its lines of electromagnetic force, which then are concentrated by the nucleus of the buried small inductor, thus creating a transformer of open magnetic current.

The buried electronic device is 1 to 2 cm. long, with a diameter of 1 to 2 mm. The displayed power, which is only a few watts in the inducting circuit, is not more than a few milliwatts for the induced current.

This general technic is suitable for many gadgets, and, if the occasion arises, it can be completed with transistors, etc. Thus, it is possible to produce local stimulation with greater accuracy and to repeat it for many years. If necessary, it is very easy to withdraw the buried small inductor from the tissues. Experiments on the sciatic nerve of a rabbit which, for two years, had been exposed to stimulation thousands of

(Continued on page A-88)

Documentary Case History . . .

Hypertension controlled for four years with Serpasil®

(reserpine CIBA)

K. C., a 67-year-old retired shirt manufacturer, had a 16-year history of hypertension, was troubled by recurrent dizzy spells and headaches. "I'd get several attacks a day. . . . Usually I'd go into the bedroom and lie down." Serpasil therapy was started four years ago, effecting a gradual reduction of the patient's initial blood pressure of 220/120 mm. to the present 140/80. Now well and asymptomatic, ". . . I'm able to go to matinees and see some of the TV shows."

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ELIXIRS, 1 mg. and 0.2 mg. Serpasil per 4-ml. teaspoon.

PARENTERAL SOLUTION: *Ampuls*, 2 ml., 2.5 mg. Serpasil per ml. *Multiple-dose Vials*, 10 ml., 2.5 mg. Serpasil per ml.

Hypertension controlled through

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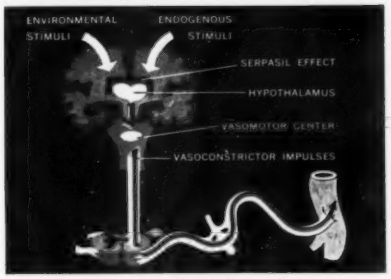
Serpasil shields the psychic and somatic reaction centers from emotional and environmental stress stimuli, thereby inhibiting the discharge of vasoconstrictive impulses through the sympathetic nerves.



Adapted from Moyer, J. H., Dennis, E., and Ford, R.: Arch. Int. Med. 96:530 (Oct.) 1955.

C I B A SUMMIT, N. J. 8/2533MK

times showed only that the myelin sheath of the nerve continued to be undamaged beneath the electrodes.

Use of inductors as hearing aids—In the field of applying inductors as hearing aids, Dr. Djourno's first attempts date back to 1953. But it was only recently that a report was published in *La Presse médicale* of his first attempt to treat a totally deaf person who previously had been operated on for cholesteatoma in both ears. The audiogram revealed that the patient had no perception of sound. During operation to graft the facial nerve, the small inductor was buried on the right side. At 1 cm. of the primary inductor, this device registered tension points in the order of 1 V, and it showed a resistance of times 10 ohms when the current was continuous.

In this case, in the presence of a greatly changed area of tissue, it was very difficult to place the metal wire against the tiny segment of nerve visible through a breach in the labyrinth. The small inductor was sunk into the temporal muscle, to which the indifferent electrode was connected. There was no leakage of cerebrospinal fluid.

The day after the operation, the patient registered a continuous whistling noise, which disappeared in two days. On the fourth postoperative day, therapeutic experiments were started. The frequencies of a few hundred stimulations per second provoked sensations which were rather unpleasant and rough. Above 1000 cycles, there was a state of total confusion, and the patient felt pain.

Speech was transmitted by means of a microphone and an amplifier feeding into the primary inductor. At first, it was unintelligible; however, certain simple words caused entirely new kinds of auditory sensation, which were quickly identified. In spite of the distortion, the patient gradually began to understand many words. He was hampered by a "background metallic voice," which often blurred the understanding of speech. Now, even when he hears the banging of a door, the patient is pleased when he lets the apparatus function. However, an accidental knock against the microphone is still felt as a painful and deafening noise.

Due to a break in the wire mass, the apparatus stopped working during the first few weeks, and it had to be replaced. However, the enforced period of silence and the additional small amount of surgery required did not result in any loss in the already acquired hearing ability.

Viral hepatitis with jaundice—Recent articles in *La Presse médicale* have discussed the successful use of metacortandracin in the treatment of viral hepatitis with jaundice at military hospitals in Casablanca and Fez, Morocco, during an epidemic among the garrisons of the two cities. The A virus was the responsible organism; laboratory tests excluded any possibility of *Leptospira* and *Salmonella* infections. All of the 457 reported cases were benign or of moderate severity, with only one fatality, one case of inflammation of the brain and eight recurrences.

The onset of the infection resembled an ordinary influenzal attack with headache and, especially, with violent and steady lumbar pain; jaundice developed on the fourth day. No itching or joint pain occurred, and the lymph nodes were only slightly affected. There was moderate enlargement of the liver but rarely of the spleen. Some patients had nosebleed and purpuric spots.

Renal symptoms were common, with temporary appearance of protein in the urine. The blood studies showed a decrease in the number of white blood cells and an increase in the mononuclear cell count. Chemical examination of the blood revealed a moderate rise of between 30 and 120 mg. of the bilirubin level, with an average rise of 70 mg. The prothrombin level decreased to almost 65 per cent of its normal value. Liver function tests were inconsistent and in no way characteristic. The jaundice lasted about 10 days; the patients were hospitalized for 40 days.

All patients were given methionine, cholagogue extracts of plants and a solution of sodium salts, and were put on a diet of the Patek-Morrison type. In addition, 100 patients also received metacortandracin. Of these, one group received the drug for 10 days in doses decreasing from 30 to 10 mg., while a second group received it for 30 days. Individual patients in the first group received a total dosage of 220 mg.; each patient in the second group received 600 mg.

The following conclusions were reached: Treatment with metacortandracin yielded distinctly favorable results. The 10 day course was as effective as the protracted medication. After the second day of treatment (as compared with 8 to 10 days in the control group), the general condition of the patient showed improvement; fatigue and anorexia completely disappeared, and the icteric discoloration began to fade. The patient's temperature dropped almost at once.

Urinary changes occurred much earlier in the

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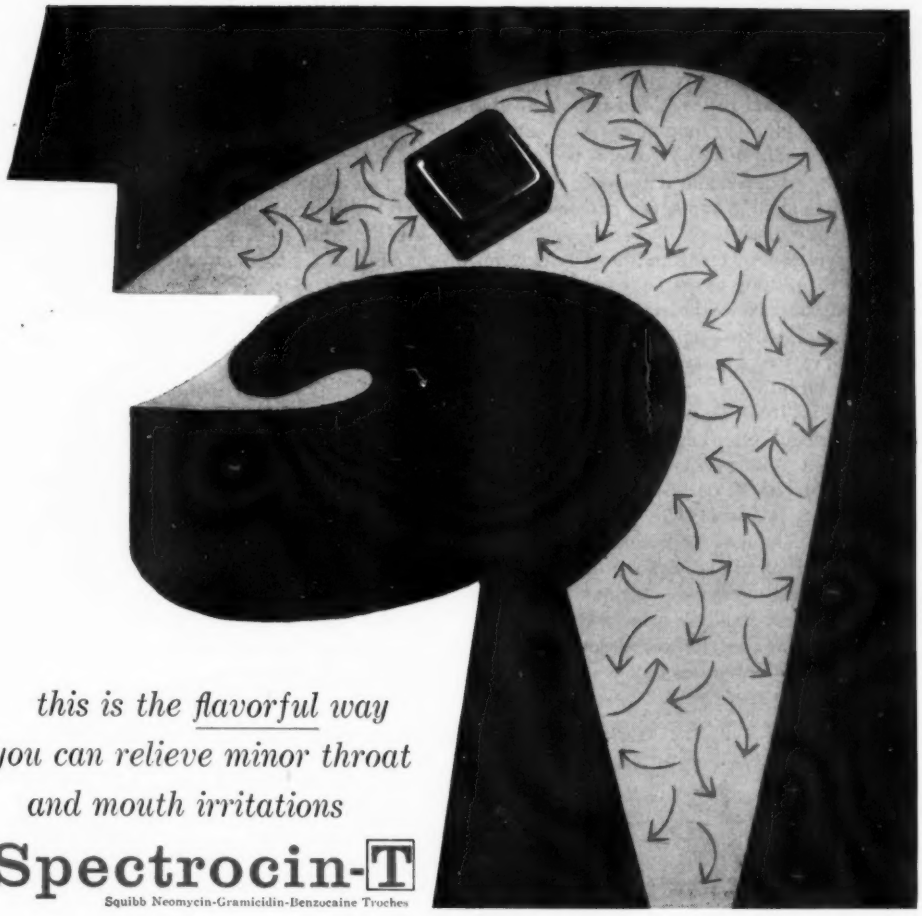

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and . . . for topical antibacterial action that really gets to the site of the infection . . . *use*

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OINTMENT 15 and 30 Gm. tubes

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study group than in the control group. The urine cleared and the feces regained their normal color twice as quickly. However, the abnormal chemical values in the blood took more time to change —the bilirubin level in the blood remained high even after the jaundice had faded and in spite of the crisis in diuresis. Only one of the patients treated with metacortandracin had a relapse, while in the control group seven persons had recurrence of the disease.

It is evident that metacortandracin quickly improves the condition of patients with viral infectious jaundice. Nevertheless, though the drug prevents complications, patients should be kept under observation for substantially the same period as before.

Changes in liver tissue during skin diseases—By means of needle biopsies, Professor Claude Huriez and his associates (Bull. Soc. franç. dermat. et syph. 64:234, 1957) have studied the changes in liver tissue which occur during some skin diseases, including certain types of eczema and psoriasis. Among the cases of eczema, he distinguishes constitutional types and cases which result from sensitization. The first group corresponds with atopic dermatoses; the second with allergic diseases of the skin that will produce positive skin tests. The needle biopsies showed nothing abnormal except in persons who have disease of the liver or inflammation of the biliary ducts and gallbladder, or are alcoholic.

However, the eczemas were complicated with gross disorder of the liver in those patients who are allergic to many things, and in those who, without being truly allergic, will react unfavorably to almost all of the internal and external medicaments, such as the antibiotics, the sulfonamides and the antihistamines. The lesions in the liver were most advanced in cases of eczema caused by poisoning with gold and arsenicals. Lipoidosis, granular degeneration of the protoplasm of the hepatic cells, almost complete disappearance of the reticulin, swelling of the Kupffer cells, and even necrosis were found.

Liver lesions are rare in children who have psoriasis, but the lesions appear to be particularly frequent among adults who have received protracted and intensive medicinal treatments.

Although it does not follow from these observations that liver lesions are responsible for skin diseases, the authors are puzzled by cases of hepatic lesions in nonalcoholic subjects who, without any clinical sign of hepatic disease, still have a distinctly affected liver.

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DR. ARTHUR G. SULLIVAN MEMORIAL LECTURE

Surgical Lesions of the Upper Abdomen

WALTMAN WALTERS* AND GEORGE A. HALLENBECK†

Mayo Foundation, Rochester, Minnesota

To honor the memory of Dr. Arthur G. Sullivan, who was Managing Director of the Interstate Postgraduate Medical Association for the 17 years preceding his death in 1954, the Association has established the Arthur G. Sullivan Memorial Lecture as a part of the program of its annual assemblies. First recipient of the lectureship was Dr. Waltman Walters, who was assisted in his presentation by Dr. George Hallenbeck.

BEFORE beginning the presentation, I should like to make a few remarks about our friend, the late Dr. Arthur G. Sullivan. May I also say that my colleague, Dr. Hallenbeck, and I feel deeply honored to present this first Arthur G. Sullivan Memorial Lecture before this Postgraduate Medical Assembly.

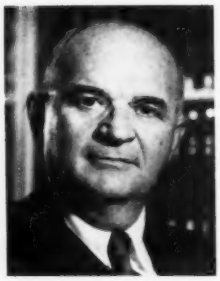
Having been one of your speakers for almost 30 years, I have seen and admired the able way in which the board of trustees, with Dr. Sullivan as managing director for more than 17 years, continued the traditions of the International Postgraduate Medical Assembly along the lines laid down by the original director, Dr. William Peck, and his board of trustees. I am very happy to say that two members of the original board of trustees are here today: Dr. Henry G. Langworthy and Dr. Tom B. Throckmorton.

These men were responsible for this method of bringing postgraduate medical education to the physicians of the United States, and the success of this venture was attested to by the development of smaller but successful regional assemblies of similar type.

Dr. Sullivan was a product of the University of Wisconsin, a graduate in medicine of Columbia University, a founder-member of the American Board of Surgery, and a fellow of the American College of Surgeons. He made many scientific contributions to surgery, among which was his research on stricture of the common bile duct. As you remember, he devised a short rubber tube with oversized catheter rings to hold it in place so that it would remain fixed in biliary-intestinal anastomosis. The name of the device is the "Sulli-

*Professor of Surgery; †Associate Professor of Surgery and Physiology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minnesota.

Presented before the forty-second annual Assembly of the Interstate Postgraduate Medical Association at Chicago.



WALTMAN WALTERS

GEORGE A. HALLENBECK

van tube," which has continued to be used effectively in managing these conditions.

Dr. Sullivan's great contribution to surgery, however, was his long service with the board of trustees of this Association in contributing to the advancement of medical education. They brought to this Assembly the leaders in medicine who were able to evaluate recent developments in medicine and surgery; but more than that, they provided the results of their own experiences with other methods of therapy and evaluated them for you as practical methods of treating the ill.

I should be remiss indeed if I did not call attention to Dr. Sullivan's contribution toward originating the journal POSTGRADUATE MEDICINE, which currently has a circulation of more than 30,000. He was managing editor for seven years. The journal was established in 1947. I am sure all of you will be happy to know that this year the editor-in-chief, Dr. Charles W. Mayo, and his editorial board were honored by the journal's being selected by the American Medical Writers' Association as the best of its class in the country.

Finally, since it is ever true that as our leaders pass on, others take their places, we note that such a change is going on in this Association. It is certainly true that we miss our old friends and colleagues; but they are happy, I am sure, to see with what hope and vigor their successors are continuing the fine work which meant so much to them, to us, and to our patients.

We have now the pleasure of presenting four cases to you.

Through the cooperation of our good friend Dr. Walter Maddock, professor of surgery at Northwestern University Medical School, and with the aid of one of his residents, Dr. Idris, we shall see today four people who have most kindly consented to appear here and allow us to discuss their histories. After that, we shall ask each one if he will excuse us while we discuss the scientific and medical aspects of his condition.

I shall briefly abstract the history which Dr. Maddock gave me of the first patient.

This man is 40 years old. Six weeks before he was operated on initially, he experienced swelling of the abdomen. He was operated on; ascites and what was termed a "black liver" were found. After this he had a mild degree of painless jaundice. Fluid continued to accumulate within his abdomen. It was necessary to carry out paracentesis, usually twice a week, and from 3000 to 6000 cc. of straw-colored fluid was obtained each time. The liver and spleen were enlarged.

The patient was operated on again and a portacaval shunt was established on July 15, 1955. The size of the spleen was four times normal; the size of the liver was three times normal. Portal pressure measured in a vein in the mesentery of the jejunum was 360 mm. of water.

Convalescence was uneventful. Whereas he formerly had to undergo abdominal paracentesis twice a week, this procedure was performed only once after his operation. Results of tests of hepatic function have indicated improvement, and he is as you see him.

Dr. Hallenbeck, in presenting this gentleman to this group, what do you think it is important to emphasize?

DR. HALLENBECK: Portacaval shunting, or the operation of joining some branch of the portal system to the vena cava, is carried out for one purpose only, so far as I know; that is to try to reduce the pressure and the venous congestion in the portal system.

Despite several opinions to the contrary and the controversy on the subject, I think the operation is useful for persons who have bled from esophageal varices when these are associated with portal hypertension, whether the

disease is caused by cirrhosis of the liver or by thrombosis of the portal vein. In this patient the operation of an end to side portacaval shunt was done in an effort to stop ascites, and the patient has not had ascites since the operation.

It is true that there is controversy as to whether a portacaval shunt is helpful in the treatment of ascites. I think this much can be said: Whatever role portal hypertension may play in the genesis of ascites, that role is relatively minor. As a matter of fact, patients who have normal livers and who have portal hypertension on the basis of thrombosis of the portal vein typically do not have ascites. Other factors, such as retention of sodium, probably are more important in this problem; certainly many cases have been reported in which portacaval shunts did not favorably influence ascites. Also, ascites sometimes abates spontaneously or as a result of good medical treatment in people with disease of the liver. Hence, it is difficult to tell in a given case whether the shunt is really responsible for any remission which may ensue.

Perhaps I can summarize it by saying that in our own institution, although we use portacaval shunting in an attempt to control the bleeding in selected patients who have disease of the liver and who have bled from varices, we have not been routinely advising shunting for patients with ascites; in fact, we have used it only once or twice in this situation.

DR. WALTERS: Dr. Hallenbeck, what is the mortality rate associated with portacaval shunts in patients with ascites?

DR. HALLENBECK: Studies by Blakemore and by Linton have indicated that in those patients who have chronic ascites (ascites which does not respond to medical treatment) the operative mortality rate after portacaval shunting has been approximately 50 per cent.

DR. WALTERS: And how does that contrast with the mortality rate when the shunts are done for bleeding esophageal varices?

DR. HALLENBECK: In people who do not have ascites and who have bled?

DR. WALTERS: Yes.

DR. HALLENBECK: With proper selection of patients the mortality rate should be somewhere between 10 and 15 per cent, and even better figures have been reported.

DR. WALTERS: I suppose that is due to the obvious hepatic decompensation, of which ascites is often an indication?

DR. HALLENBECK: Yes, patients with chronic ascites usually have less hepatic reserve.

DR. WALTERS: I do not do portacaval or splenorenal shunts. Dr. Hallenbeck has done almost all of them in our institution, so I am acting for you, I think, in asking him these questions.

When should a portacaval shunt be done and when should a splenorenal shunt be done? What are the advantages of each?

DR. HALLENBECK: Let us limit the question to apply only to patients who have cirrhosis, if we may.

DR. WALTERS: Yes.

DR. HALLENBECK: I think the end to side portacaval shunt undoubtedly provides the most complete decompression of the portal system of any operation known to us now. However, in patients with cirrhosis the operation is followed by a higher incidence of severe neurologic symptoms requiring the use of low protein diets, and sometimes these symptoms will not yield to such measures.

In recent years we have preferred to do the splenorenal shunt if the splenic vein is large enough to provide a basis for a really good shunt. We estimate the size of the splenic vein immediately before the operation by obtaining a splenic portogram, meaning that we inject some UROKON® sodium or similar radiopaque substance percutaneously into the spleen and take a roentgenogram about five seconds after the injection or, actually, during the last part of the injection. Thus we gain some impression of how large the splenic and portal veins really are.

DR. WALTERS: Now, let us say this patient has acute hemorrhage. You know, without going into detail, that the site of the bleeding is esophageal varices. How do you manage it? Could any of us do it? How did you do your first one?

DR. HALLENBECK: We use the balloon tube called the Sengstaken-Blakemore tube. Any of you could use it. I think the key to the situa-

tion in the bleeding cirrhotic patient is to put the tube down early, and not to delay for a couple of days in the hope the bleeding will stop. Such a delay contributes to death of the patient.

The first time I used such a tube I opened the container, read the directions printed clearly therein, and installed the tube. I am sure any physician can do it.

DR. WALTERS: How soon after the bleeding is controlled is it advisable to proceed with the shunt?

DR. HALLENBECK: That would depend, of course, on how much evidence of hepatic insufficiency has developed. The interim would vary from as little as a week in the presence of rather modest hemorrhage to sometimes three, four or five weeks or even longer in the presence of serious bleeding.

DR. WALTERS: Can a general surgeon learn this technic of vascular anastomosis; if so, how can he practice it?

DR. HALLENBECK: I think any well-trained general surgeon could learn to do it. The problem would be not so much learning the technic as accumulating enough experience with various patients to be certain of the decisions he has to make, such as on whom to operate and when to avoid operation. If the surgeon previously has not done any vascular surgery, he would be very well advised to obtain some experience with vascular anastomosis in animals before he proceeds to more formidable interventions.

DR. WALTERS: I might add to that, as some of you know, that the late Dr. Robert Coffey, after finishing his work in the operating theater in Portland, would have the intestines of swine brought into the operating room and would practice anastomoses. I am sure all of you know the effectiveness of practicing these vascular procedures on animals before the procedure is applied to human beings. Dr. Blalock did many vascular anastomoses between the subclavian artery and the pulmonary vein in animals before he performed the procedure first on a "blue baby."

The second patient is a woman who has had two insulinomas removed from her pancreas. Her history is typically that of a patient with hyperfunctioning islet cell adenomas, that is, at times she would become weak, feel faint, and even lose consciousness. It was said that sometimes she would have convulsive movements. When she was given fruit drinks or wine she would immediately revive. These attacks could be prevented by giving her sugar in one form or another.

During her period of observation in the fasting state she went into coma and the blood sugar was found to be 39 mg. per cent. She was given glucose intravenously and revived immediately. What is that called?

DR. HALLENBECK: The Whipple triad. First of all, the attacks arise when the patient is fasting. Second, if a determination of blood sugar is made while the patient is experiencing an attack, it will be found to be less than 50 mg. per cent. Third, the symptoms are immediately relieved by the intravenous or oral administration of glucose.

DR. WALTERS: Tell us about factitial hypoglycemia.

DR. HALLENBECK: I think you refer to the state of the people taking insulin?

DR. WALTERS: Yes.

DR. HALLENBECK: That is an unusual phenomenon, one that might not be remembered if the physician had not seen it. Several patients have been shown to have true hypoglycemia; some have even undergone surgical exploration, done in an attempt to find islet cell tumors, and later have been found to be taking insulin themselves to induce hypoglycemia. If there is any suspicion of such malingering, a search can be made of the patient's room for syringes or insulin. Have you ever seen such a patient?

DR. WALTERS: Yes, I have. I operated twice on such a patient, a very attractive girl with a Master of Arts degree who was an outstanding social-service worker in her community. She was later operated on and no tumors were found. She subsequently died in hypoglycemic shock; at postmortem examination adenomas were not found, but a hypodermic syringe and insulin were found hidden in her luggage.

DR. HALLENBECK: I wish to ask this patient one question, Dr. Walters. Before you underwent operation, did you realize that if you ate

something during an attack you would be perfectly all right?

PATIENT: No, I never had that happen.

DR. HALLENBECK: I think that this is atypical. Many people in such circumstances will discover that eating makes them feel better, and they will become rather heavy because they continue to apply the discovery.

DR. WALTERS: I should like to explain to this lady before she goes that the episodes of crying she had during the preoperative period at the time of an attack are often seen as simply neurologic manifestations of hypoglycemia.

Thank you for coming. The result of your operation is gratifying indeed.

One of the most interesting papers on insulinoma was that by Howard, Moss and Rhoads from the University of Pennsylvania, published in 1950 in *International Abstracts of Surgery*. They collected 398 cases of insulinomas, 224 of which were removed at operation. We have had a group of 91 patients who were described by Breidahl, Priestley and Rynearson. As these patients were cared for, a procedure was developed for exploration and operative treatment of those suspected of having islet cell tumors. Dr. Hallenbeck will discuss it.

DR. HALLENBECK: The islet cells in the pancreas are distributed in such a manner that about 75 per cent of them are in the body and tail and about 25 per cent are in the head. Islet cell tumors follow somewhat the same distribution (table 1). In this particular group of patients, 25 per cent of the lesions were situated in the head, and the remainder were in the body and the tail, except for a few multiple lesions.

Over the years at our institution, the following policy or method of ministering to patients with hypoglycemia has been developed. First, it must be absolutely certain that the patient really has hypoglycemia caused by islet cell tumor. Once that certainty is established, the surgeon opens the abdomen, explores the pancreas, and, if he finds a tumor, removes it. In our experience a tumor has been found in 70 per cent of patients.

If, after thorough exploration, a tumor cannot be found, the body and tail of the pancreas are removed. The operation is concluded at that point. A period ensues during which the patient is observed to determine whether or not this procedure has prevented the attacks of hypoglycemia. In many specimens of tissue removed at such an operation, a microscopic tumor too small to be felt grossly will be found by the pathologist. In a few patients symptoms will persist, and it is then that the next step is taken. This step is careful reexploration of the head of the pancreas in a search for a tumor which is simply to be removed. If, again, none is found and if the symptoms are severe enough to warrant it, the Whipple operation is done to remove the head of the pancreas.

TABLE 1

SITE OF ORIGIN OF ISLET CELL TUMORS IN THE PANCREAS IN 76 PATIENTS*

	NUMBER	PER CENT
Head	19	25
Body	22	29
Tail	28	37
Junction of body and tail	4	5
Multiple	2	3
Not stated	1	1

*From BREIDAHL, H. D., PRIESTLEY, J. T. and RYNEARSON, E. H.: Hyperinsulinism: Surgical aspects and results. Ann. Surg. 142:698-706 (October) 1955.

Have you ever been confronted with the necessity of performing the Whipple operation, Dr. Walters?

DR. WALTERS: Yes, I recall three such cases. In two of them our colleague, Dr. Waugh, did the operation. Subtotal pancreatectomy previously had been performed, but the symptoms persisted. A Whipple operation was done later, with removal of the first and second portions of the duodenum, the head of the pancreas, and the lower part of the common bile duct. But I was fortunate, a few weeks ago, in finding an adenoma situated above the duodenum in the remaining small segment of the head of the pancreas in a patient who previously had undergone subtotal pancreatectomy. Hence, let me urge you to search the head of the pancreas very carefully before resorting to the Whipple operation.

Dr. Hallenbeck, I should like to ask two or

three questions. In what percentage of cases of adenomas will the tumors be found in the body and tail of the pancreas?

DR. HALLENBECK: Approximately 75 per cent are situated in the body and tail of the structure.

DR. WALTERS: What per cent of lesions are multiple?

DR. HALLENBECK: I have seen a figure of 6 to 8 per cent given as applying to the incidence of multiple lesions.

DR. WALTERS: The next patient is a woman 70 years old. She had a typical history of biliary colic, although she had no evidence of obstructive jaundice or obstruction of the bile duct. She did have fever, but without jaundice or chills.

She was operated on. Multiple small stones were found in the gallbladder; the cystic duct and common bile duct were enlarged. The common bile duct was opened, and two small stones were found in it.

An operative cholangiogram was made. No more stones were seen. The dye proceeded into the duodenum satisfactorily. The T tube was sutured in place and was removed 10 days later, after a cholangiogram had been made which showed a normal bile duct emptying normally. Do you wish to comment on this case?

DR. HALLENBECK: When should the common bile duct be explored? Here is an instance in which exploration was done because of three indications: First, many small stones were found in the gallbladder; second, the cystic bile duct looked large enough to allow a stone to pass through it; third, there was some slight degree of dilatation of the common bile duct, although, as I understand it, not much.

Two absolute indications for exploration of the common bile duct are (1) the presence of jaundice, chills and fever before the operation, and (2) the presence of a palpable stone in the common bile duct at the time of operation. In itself, simple enlargement of the common duct with no evident reason is a very important reason for exploring the common bile duct. Many times stones will be found when simple enlargement is present.

DR. WALTERS: I think that last point is very important. It should be emphasized: Every enlarged common bile duct should be opened and explored with scoops for the presence of stones. The duct also should be irrigated. If no stones are found an attempt should be made to ascertain the cause of the enlargement of the duct. Has the stone passed? If so, the sphincter of Oddi would be expected to be dilated so that an 8 mm. scoop could be passed into the duodenum readily. This sometimes happens. Does the patient have edema of the head of the pancreas which has narrowed the pancreatic portion of the common bile duct? If so, the enlargement, thickening and edema in the head of the pancreas can be felt. Is there a question of carcinoma of the ampulla or of the papilla? If so, action should be taken, for sometimes, when the situation is uncertain, particularly in elderly people who have lost weight and may have had a degree of anemia, it is worthwhile to open the duodenum and carefully inspect the region of the ampulla.

Some years ago Dr. Landry and I reported five such cases in which small malignant lesions of the ampulla were found only when the duodenum was opened.

This brings up the question of operative cholangiography. Do you use operative cholangiography? If not, why?

DR. HALLENBECK: I do not use it, Dr. Walters. I think that we have had rather good success in that we have missed very few stones in those ducts that we have explored surgically. True, I have missed some stones; every surgeon misses some at times. Actually, the number missed does not seem to exceed what I judge is the error inherent in the operative cholangiograms.

Another point: How about the ducts which are not explored but which contain stones which might have been found and removed had a cholangiogram been made? The point is tenable, but to judge by the subsequent course of the patients concerned, I seem not to have encountered a sufficient number of untoward instances to cause me to use the technic, Dr. Walters. What about your experience?

DR. WALTERS: I have the same opinion. However, one of our surgeons has made a study of a series of operative cholangiograms

that were made for 200 patients, and the important consideration is that in the first 25 cases, several cholangiograms had to be discarded because of inaccuracies brought about by faulty technic. However, Drs. Ferris and Weber took the 200 cases, discarded 15 because of technical errors, and considered the remaining 185. In only seven cases did they find stones which they had not suspected were present. Dr. Hallenbeck, do you care to comment on this observation?

DR. HALLENBECK: The technic of making cholangiograms with the source of the x-ray apparatus rather close to the patient as a rule tends to make the ducts look enlarged in relation to their actual gross appearance. I find it somewhat difficult to decide by means of a cholangiogram whether some ducts which seem to be enlarged actually are enlarged.

DR. WALTERS: I will stand on the statement that I have made repeatedly here: I have never seen a stone larger than a few millimeters in diameter in the common bile duct not accompanied by enlargement of the duct, and I have opened a great many ducts of small size associated with small stones in the gallbladder and cystic duct but without stones in the common bile duct.

Although we shall not be able to present the last case in as much detail as we would like, we shall do the best we can.

DR. HALLENBECK: The patient has had duodenal ulcer. On one occasion, because of some degree of bleeding, I believe, she underwent gastroenterostomy. The stomach did not empty well after the operation, and somewhat later entero-anastomosis was performed. The two loops of jejunum leading to and from the stomach were sutured together side to side, and the stomach then emptied satisfactorily.

Subsequent to that procedure a gastrojejunal ulcer developed, which caused the formation of enough scar tissue to obstruct the transverse colon. This problem was managed by an operation which I think was beautifully conceived and which must have been very difficult. The following surgical measures were accomplished: (1) About two-thirds of the stomach was removed and the gastric remnant was sutured to the duodenum (*to the duodenum*, that is, a Billroth I operation); (2) the aperture in the jejunum to which the stomach previously had been attached of course was closed; (3) that portion of the transverse colon which had been the site of the stricture and a part of the colon that had been adjacent to the gastrojejunal ulcer were taken out and the two ends of the colon were joined together; and (4) bilateral vagotomy was performed. The patient withstood the operation well, but since that time another ulcer has developed at the gastroduodenal junction.

DR. WALTERS: I think the important point to emphasize is that this patient exhibits a greater tendency to form peptic ulcers than the usual patient does. The development of the gastrojejunal ulcer after gastroenterostomy followed the performance of entero-enterostomy between the proximal and distal loops of jejunum. This procedure deviates alkaline secretions from the duodenum away from the site of gastrojejunostomy and increases the likelihood of an ulcer's forming there. For this reason, the operation should be avoided. Yet, even after performance of what would ordinarily be an adequate subtotal gastrectomy coupled with vagotomy, a new ulcer formed. It is to be noted that gastrointestinal continuity was re-established by gastroduodenostomy.

Studies that two of my assistants and I have made in patients who have undergone gastric resection and gastroduodenostomy show that the incidence of recurrent ulceration is higher than in patients who have undergone comparable resection and gastrojejunostomy. Yet, this patient also underwent bilateral vagotomy, which one might expect to offer added protection against recurrent ulceration. Our experience with this combination is too small to allow us to draw conclusions concerning it. The completeness of vagotomy could be determined by the insulin (hypoglycemia) test; even in the best of hands, vagotomy occasionally is incomplete. Another possibility is that our patient might have one of the pancreatic tumors described by Zollinger and associates as sometimes accompanying recurring peptic ulcers.*

*It was, in fact, subsequently learned from Dr. Maddock that this patient proved to have a pancreatic tumor.

Clinical Importance of "New" Respiratory Viruses

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WHEN I started in virus research some 10 years ago, the undifferentiated and respiratory disease problems seemed rather simple. This was not in the sense that it would be easy to find out what was going on; we expected that to be difficult. But it did seem that after we had delineated the streptococci and the influenza virus and psittacosis and Q fever and other agents with respect to the various respiratory problems they caused, we needed to find only three additional viruses. One was the "common cold virus," responsible for the afebrile respiratory disease that some people seem better able to define than we. Another was the virus responsible for the acute febrile disease (ARD) entity, in which fever, of course, is the characterizing sign. The third condition on the list was primary atypical pneumonia. Now, 10 years later, we face the paradox that, while the problem is not simple but is extremely complex, the demonstration of viruses has become very commonplace. In fact, it is difficult to work in the virus field for any appreciable period without encountering a new virus.

I can imagine how confusing the present situation must be for the practicing physician when both the virologist and the specialist appear confused, and what his reaction must be when very often he reads about new viruses for the first time in newspapers; last week a paper on a new virus appeared for the first time in *The New York Times*—the full manuscript! Anyway, the practitioner must have quite a time trying to cope with ECHO viruses, adenoviruses, Coxsackie viruses, and other agents called JH, CA, ARD, APC and so forth.

It would be easier for me to ignore the complex problem of numerous different viral in-

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fections and talk about some of our more interesting laboratory findings. But, for better or worse, I shall try to give you something of the total picture—an incomplete picture, to be sure, but one I hope will be helpful.

Grouping most of the newly recognized viruses in large categories, there are the "enteroviruses" consisting of the Coxsackie viruses (some 24 at present), three polio viruses, and 20 or more ECHO viruses. Then there are the respiratory viruses, the adenoviruses (18 at present), and other viruses known as JH, CA ("croup associated") and certain syncytial viruses. Including still other viruses that are well established but still not classified, the total comes to 75 newly recognized viruses that have been uncovered in the past 10 years. This is quite a harvest, considering that Rivers' latest textbook on virus diseases reported only 60 distinct virus agents. True, many are very similar, but each is a separate example of a prevalent virus, transmitted, for the most part, from person to person. Most people apparently get most of them eventually if they live long enough. They generally cause nonfatal illnesses, the viruses having learned to live with their human hosts and vice versa. They represent, at least in this country and certainly in most urban and suburban areas, possibly the major remaining infectious disease problem, viewed in toto. Certainly from the general practitioner's and pediatrician's standpoint this is anything but an extreme statement.

We have learned something about what these viruses do. We need to learn more. The Coxsackie viruses have been shown to cause a number of illnesses, some of them well characterized and others not so well characterized. Eight of the Coxsackie viruses cause an illness known as herpangina. This has been reported extensively in the literature and is familiar to all of you. Two of the Coxsackie viruses, types 7 and 9, cause a nonbacterial meningitis; the Russians have described the former as polio virus type 4.

Group B Coxsackie viruses cause epidemic pleurodynia or Bornholm disease. This is not so uncommon a disease after all, now that we are alerted to look for it. In recent years it has been particularly common in nearly all parts of the world. Group B viruses also commonly cause a nonbacterial meningitis with or without pleural or abdominal pain. More recently, investigators in several different parts of the world have isolated several of the Coxsackie B types from the heart muscle in cases of fatal myocarditis in young children.

Perhaps the most frequent manifestations of Coxsackie viruses as observed in young infants are "fevers of undetermined origin" and "febrile colds." The specific disease entities such as paralytic polio, herpangina and pleurodynia represent less frequent manifestations.

At the National Institutes of Health we are engaged in a search for causes of colds as they are seen in general practice. We conclude from these rather extensive studies that one must consider the likelihood that the Coxsackie and polio viruses contribute to the picture. Representatives of both groups of viruses grow in the pharynx and nasopharynx and cause local signs and symptoms. When not attended by the more severe or specific manifestations, what else are illnesses such as these likely to be called if not fevers of undetermined origin or febrile colds?

The ECHO viruses comprise a group of 20 serotypes. This unusual name developed out of earlier terms, enteric cytopathogenic human orphans. Drs. Sabin and Hammond called them enteric viruses; Dr. Melnick called them orphan viruses. They have not been studied intensively enough yet to know what all of them do, but at least five types (4, 6, 9, 14 and 16) have been associated with aseptic or nonbacterial meningitis. Types 9 and 16 also have been found to cause a rubelliform rash disease. This illness was quite epidemic in Europe in 1956, and in 1957 it occurred in epidemic form in our Middle West, particularly in Wisconsin.

Sabin has reported type 10 and a closely related virus in a common coldlike illness in chimpanzees and in children with diarrhea.

During the past two years we have observed several additional ECHO viruses occurring in an orphanage nursery in Washington, D. C. About 25 per cent of the children in the nursery are replaced each month. They range in age from six months to three years and have

astonishingly high rates of acute febrile respiratory and other undifferentiated illnesses. Approximately 10 ECHO viruses have occurred during the two year period of observation. Although several hundred infections have occurred, we have observed only very mild illnesses in relation to them. At most, we can attribute on the average no more than one day of fever per infection. The pediatrician in attendance usually describes the coincident illnesses as febrile colds.

Now for the respiratory viruses. At present some 18 different adenoviruses have been isolated from humans, and almost half as many from monkeys and chimpanzees. The various human adenoviruses have differing epidemiologic patterns in the general population and are known to cause at least five distinct respiratory and ocular illnesses.

Although our research group at the institute demonstrated the first adenoviruses, Hilleman and Werner at the Army Medical School demonstrated the first illness caused by these agents. Acute respiratory disease (ARD) is a distinct entity that has been well described by the Armed Forces Respiratory Commission in studies of illness among military recruits. The prevalence of ARD among recruits can be very high; sometimes as many as 50 per cent will have the illness during their first few weeks of training. The serotypes causing most of this illness are types 4 and 7, with 3 and 14 being the next most frequent types.

Acute respiratory disease characteristically occurs epidemically. It can be followed by pneumonitis, an atypical pneumonia without cold agglutinins.

Pharyngoconjunctival fever, a specific illness, usually occurs in epidemics. It was probably first described in Australia by Derrick, and several years ago Cockburn in Denver reported it. The illness occurs mostly in children and is caused chiefly by types 3 and 7. However, types 1, 4 and 5 can also cause it. Sequelae are pneumonitis, particularly in the winter, and, rarely, a superficial keratitis in summer.

Nonbacterial pharyngitis, an illness very like pharyngoconjunctival fever but without conjunctivitis, is perhaps the most common illness caused by adenoviruses. It occurs chiefly in infants and very young children. Types 3 and 5 can cause it, but types 1 and 2 most frequently are responsible. Until recently we did not have sufficient information to establish that types 1, 2 and 5 actually cause the illness, but recent data soon to be published establish them as frequent causes of nonbacterial pharyngitis with fever.

In contrast to pharyngoconjunctival fever and ARD, nonbacterial pharyngitis is mostly endemic in occurrence. Serotypes 1 and 2 involve nearly all children early in life, so that too many older children and adults are immune to permit a good epidemic. Again, pneumonitis may occur as a sequela.

Uncomplicated nonbacterial conjunctivitis due to adenovirus occurs at all ages, but apparently it is most common among persons in older age groups. I have had this illness twice myself in two different years, caused by types 3 and 4. As is characteristic in the adult, I had virtually no fever. This localized catarrhal conjunctivitis, which most often begins unilaterally, has been reported rather extensively recently. How much of the total amount of catarrhal conjunctivitis is due to this virus, however, must still be determined.

Epidemic keratoconjunctivitis (EKC) occurred in this country chiefly during World War II among industrial workers exposed to arc welding and eye injuries. It has been fairly prevalent in Japan in recent years, and it appears to be quite prevalent in the Mediterranean area. Recent epidemics have been reported in Scotland, Italy and Germany. This illness must now be regarded as being caused almost entirely by adenovirus type 8, a serotype first isolated by Jawetz in California. EKC characteristically has an epidemic occurrence. However, sporadic cases and small outbreaks have been traced to the use of the tonometer in ophthalmologic practice. It would appear that corneal irritation is important in the establishment and dissemination of several of the adenoviruses.

To sum up the adenoviruses, types 1, 2 and 5 cause febrile pharyngitis in children. These viruses persist in adenoids and tonsils, and by growing tonsillar tissue in tissue culture

we can isolate the viruses years after the primary infections. Type 3 causes pharyngoconjunctival fever and febrile pharyngitis without conjunctivitis. Types 4, 7 and 14 cause ARD in military recruits and have been incriminated in at least one industrial outbreak. Type 8 causes epidemic keratoconjunctivitis. The clinical importance of other types must still be determined.

What do these newly recognized viruses mean in terms of the total undifferentiated and respiratory disease problems that practitioners encounter almost daily? First of all it is necessary to subtract (particularly in older persons) the psychosomatic illnesses. As general practitioners and specialists in medicine, you recognize that there are such illnesses. Another contributor to the total problem, of course, is nasopharyngeal allergy, and this must also be subtracted from the total problem. Finally, there are the microbes that cause febrile and afebrile respiratory diseases.

The role of the various viruses depends on age. For the past four or five years our epidemiologic group has been studying febrile respiratory illnesses in general populations as well as in the orphanage I mentioned before. We have been able to confirm, with much larger figures, the findings of Dingle's group and others which indicate that children experience much more undifferentiated illness than do adults. In our present studies we are concentrating on the viral causation of these illnesses in children. Although the problem is still very complex, at least we have less to worry about with respect to psychosomatic factors and allergy, although both of these factors do exist.

Contemporary analysis of our data indicates that while we can determine roughly what many viruses are doing we still must find the causes of 70 per cent or more of the undifferentiated illnesses.

Except in military recruits, the use of adenovirus vaccine in general population groups is not justified by available information. We are now planning to test adenovirus, influenza, Coxsackie and ECHO vaccines in our study populations. I personally feel that no one group virus vaccine, even if effective, will do enough good to be given generally in the near future. In order to expect to prevent sufficient numbers of undifferentiated illnesses, vaccines may have to contain as many as 20 to 30 antigens. This, I think, eventually will be technically possible.

Drug Therapy of Cardiac Arrhythmias

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DISORDERS of the rate and rhythm of the heart beat are seen frequently today by physicians in all fields of medical practice. Benign disturbances often are diagnosed and treated appropriately without the use of electrocardiograms. Occasionally, however, a patient with or without underlying heart disease is presented as an emergency; in such an instance, quick electrocardiographic confirmation of one's clinical impression may be helpful in restoring to normal the patient's cardiac rhythm and general condition. If previous electrocardiograms are available for comparison in these situations, they can be extremely valuable. With or without such help, the serious arrhythmias must be treated promptly. On the other hand, we must avoid scrupulously the chance of letting a patient become a cardiac cripple because of unrealistic anxiety over a harmless mechanism disturbance. Never forget Wilson's[1] sterling advice that the electrocardiogram always should be interpreted in the light of the total clinical picture. The doctor who is in charge of the patient is in the best position properly to evaluate the medical situation. Such evaluation should not be the responsibility of the electrocardiologist, who may scrutinize the tracings without the benefit of seeing the patient.

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We propose to review the diagnosis and

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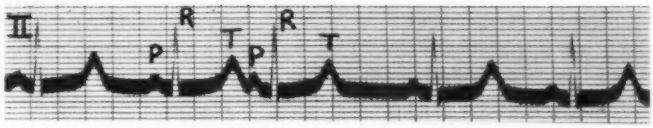

FIGURE 1. Atrial premature beat in a 54 year old man with hypoparathyroidism, normal arterial pressure and no cardiac enlargement.

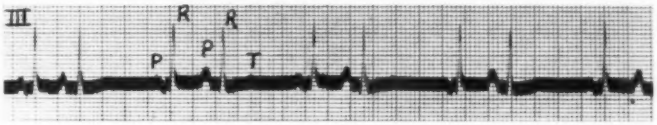

FIGURE 2. Coupling due to atrial premature beats in a 44 year old woman with chronic rheumatic heart disease, mitral stenosis and congestive heart-failure.

treatment of the common arrhythmias, which physicians are seeing more often today because of our increasingly aging population and because of more frequent use of electrocardiography in all branches of clinical medicine.

Ectopic Beats

The most common rhythm abnormalities are ectopic beats. According to the location of the pacemaker, they may be classified as atrial, nodal or ventricular premature beats. They occur in persons of all ages and in almost everyone more than 70 years of age.

Atrial premature beats—Such beats usually produce no important symptoms; they are benign, and thus often require no treatment other than reassurance. They may occur as occasional ectopic beats or there may be runs of them. Figure 1 shows an isolated atrial premature beat. The third P wave is abnormal in contour and occurs early in the normal cycle. It is followed by a QRS complex which is not remarkably different from those in the normal cycles, and the P-R interval is at least 0.12 second. After the premature beat, there is an incomplete compensatory pause; the sino-atrial node then resumes its role as pacemaker.

Figure 2 shows an example of coupling due to atrial premature beats. Here, each alternate beat is premature. Atrial premature beats occur most often in the emotionally sensitive patients; but use of coffee, alcohol and tobacco also has been associated with their occurrence. Likewise, ectopic beats of atrial origin may be seen in patients with any type of organic heart disease.

If the ectopic beats are frequent, the rhythm may be mistaken for atrial fibrillation; indeed, it may change to atrial fibrillation or to paroxysms of supraventricular tachycardia. A test of exercise may serve to abolish the premature beats; but this tends to make atrial fibrillation more irregular, thus differentiating the two. In patients with severe organic heart disease, especially in those about to have any surgical procedure, it is necessary to consider prior digitalization. For symptomatic relief, 0.2 to 0.4 gm. oral quinidine sulfate three or four times daily may be used for those patients who complain of "thumping" or "skipping" of their heart beats. If the symptoms are most troublesome at night, the use of enteric-coated tablets may avoid interruption of sleep. If severe congestive heart-failure is present, digitalization is indicated before quinidine is considered. If evidence of digitalis intoxication is present, the offending preparation should be withdrawn; and, if there is a probability of potassium deficiency, enteric-coated potassium chloride tablets in a dosage of 2 or 3 gm. three times daily is the best form of therapy, provided renal function is adequate.

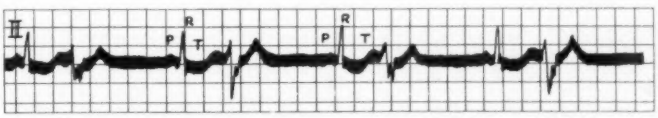

FIGURE 3. Coupling due to multifocal ventricular premature beats in a 54 year old man with a history of coronary occlusion, showing slight cardiac enlargement in the presence of normal arterial pressure.

Nodal ectopic beats—If therapy is needed in this rare condition, treatment is similar to that of atrial premature beats.

Ventricular premature beats—Occurring occasionally, especially if unifocal, ventricular premature beats are not indicative of organic heart disease. If they are multifocal (figure 3) and originate from sites in both ventricles, as seen in a given lead of an electrocardiogram, they may have more serious implications. They are often seen in patients after a myocardial infarction, and they may be a warning of a threatening episode of paroxysmal ventricular tachycardia or fibrillation. They likewise may be a reflection of digitalis intoxication and often produce coupling in this instance, as demonstrated in figure 3. By auscultation, one usually cannot differentiate them from atrial or nodal premature beats. In the electrocardiogram, alternate QRS complexes are wide and bizarre. The absence of ectopic P waves differentiates these ventricular premature beats from atrial premature beats with aberrant ventricular conduction.

For those patients without demonstrable heart disease, reassurance or, sometimes, the use of a mild sedative is all that is needed for symptoms of "palpitation," "pounding" or "somersaulting" of the heart. If the premature beats are due to digitalis overdosage, the drug should be discontinued and potassium chloride should be given in doses of 3 to 6 gm. per day for serious intoxication. If the ectopic beats are seen following a myocardial infarction, either 0.2 to 0.4 gm. quinidine sulfate or 0.25 to 0.50 gm. procaine amide hydrochloride (PRONESTYL®) four times daily should be used. If these early ventricular contractions occur often enough to cause impairment of cardiac efficiency in patients with organic heart disease but not in congestive failure, quinidine or procaine amide therapy often improves the mechanism sufficiently to produce an obvious subjective increase in myocardial reserve.

It should be emphasized that premature beats from any focus occurring in anxious, emotionally unstable people without any other evidence of heart disease are to be recognized as a nuisance and treated accordingly. To do otherwise is a certain way to make sick people out of healthy ones. The rehabilitation of an iatrogenic cardiac cripple is not easy.

Sinus Tachycardia

In this mechanism, the impulse arises normally in the sino-atrial node, but the rate is increased to 100 to 160 beats per minute in adults. Sinus tachycardia may be associated with physical exercise, emotion, certain drugs, fever or various infectious diseases. The rate tends to be variable. Carotid sinus stimulation, by slowing the rate, is useful in distinguishing this mechanism from paroxysmal supraventricular tachycardia. Figure 4 shows an example of sinus tachycardia. Normal P waves and P-R intervals are evident. When necessary, the treatment is that of the underlying disease or condition.

Sinus Bradycardia

In this condition, also illustrated in figure 4, the discharge rate of the impulses from the sino-atrial node is less than 60 per minute, and P waves occur regularly before each normal QRS complex. Sinus bradycardia often occurs in people who have normal hearts. It is a common finding in athletes, especially in long-distance runners; it is observed during sleep. It may be seen in patients with cerebral

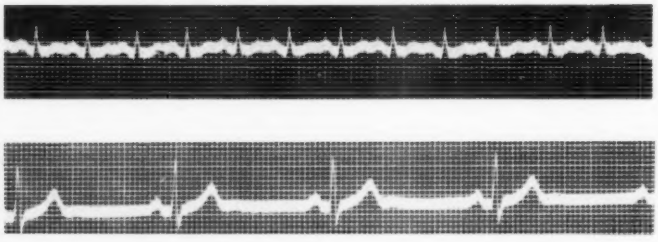

FIGURE 4. Upper tracing: sinus tachycardia in a 20 year old girl with trichinosis, showing a rate of 150 beats per minute and a P-R interval of 0.12 second. Lower tracing: sinus bradycardia in a 46 year old man with no evidence of heart disease, showing a rate of 48 beats per minute and a P-R interval of 0.16 second.

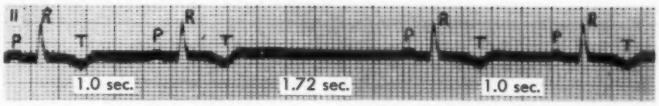

FIGURE 5. Sinus arrest. Note the long diastolic pause between the second and third complexes. The pause is not an exact multiple of the normal P-P cycle; it is 1.72 rather than two seconds in this instance.

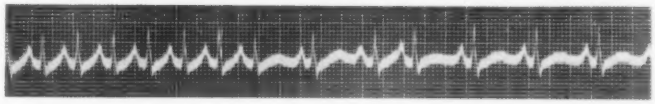

FIGURE 6. Paroxysmal atrial tachycardia in a 12 year old girl with a history of frequent attacks of rapid heart rate, the episodes beginning and ending abruptly. The lead II tracing reveals the sudden, spontaneous termination of a short attack. An atrial premature beat is shown here also.

tumors, increased intracranial pressure from other causes, myxedema, and various infectious diseases. Symptoms are uncommon, but occasionally syncope and dizziness have been reported. The underlying mechanism is probably a combination of increased vagal tone and decreased sympathetic tone or predominantly one or the other. If treatment is needed, it ordinarily is that of the underlying disease, if such is present. The bradycardia itself seldom requires the use of drugs unless syncopal attacks occur.

Sinus Arrest

Illustrated in figure 5, sinus arrest denotes failure (usually momentary) of the sino-atrial node to initiate an impulse; it is uncommon in normal, healthy persons and in those who have not received medication. The mechanism is either a direct stimulation of the medullary vagal center or a reflex vagal stimulation through the carotid sinus or other visceral afferent receptors. Electrocardiographically, it is recognized by a long diastolic pause between two normal complexes. The pause is not an exact multiple of the normal P-P cycle. It has been seen in patients after pharyngeal stimulation or gagging has occurred, or in hypersensitivity of the carotid sinus. It also may occur during use of anesthesia, during surgery, and after the administration of various drugs such as quinidine. Occasionally, if sinus rhythm does not return at once or if a lower pacemaker does not initiate rhythmic beating, a syncopal attack will occur. If ventricular contractions do not resume in this situation, the patient will die unless the physician can stimulate the myocardium by a hard blow on the chest or unless he can perform a prompt thoracotomy and begin cardiac massage.

Zoll[2] has devised an external electric pacemaker* which may be applied to the precordial area; or, if the chest is opened, the electrodes may be placed to stimulate the heart directly. This machine should be standard emergency equipment in all hospitals. It can be obtained with a companion ventricular defibrillator in the same portable case.

Sinus arrest can be differentiated from sino-atrial block by use of the electrocardiogram. In such block the impulse forms normally in the sino-atrial node, but it does not spread naturally through the atrial muscle. The longer R-R intervals produced by intermittent block will be more or less precise multiples of the basic R-R intervals. If this occurs, one should look for: (1) intoxication with digitalis, quinidine, potassium or NEO-SYNEPHRINE®, (2) a hypersensitive carotid sinus, or (3) a cerebral lesion.[3]

Paroxysmal Supraventricular Tachycardia

Either an ectopic atrial focus or the atrioventricular nodal tissue may be the origin of paroxysmal supraventricular tachycardia (figure 6). This is one of the most common mechanism disturbances requiring drug treatment, and it can be most rewarding to manage. Fortunately, it occurs most frequently in

*Electrodyne Company, Inc., Norwood, Massachusetts.

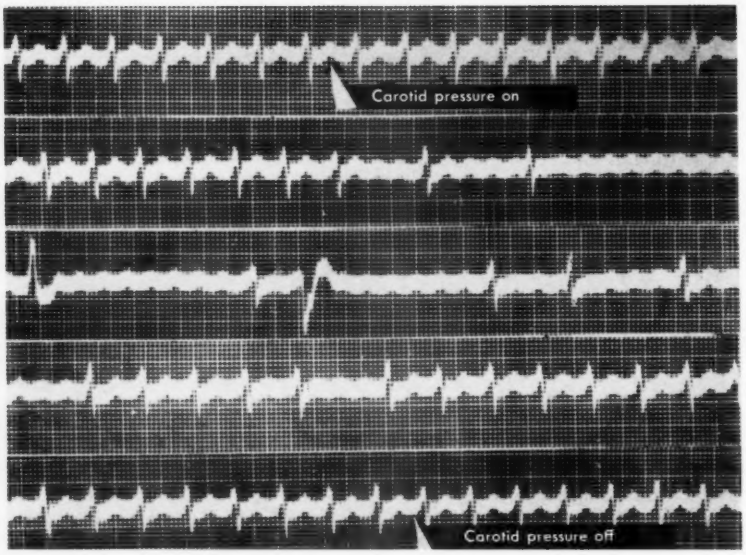

FIGURE 7. Continuous lead II tracing showing carotid sinus stimulation which temporarily increased the degree of atrioventricular block, revealing the regular atrial flutter waves and differentiating this arrhythmia from supraventricular tachycardia.

patients without demonstrable evidence of underlying heart disease and here, as with premature beats, the nuisance of the attacks is to be stressed. To be sure, this may be a frightening experience; active treatment may be necessary to terminate it, but it does not spell doom. Nevertheless, this arrhythmia may be seen in association with myocardial infarction, thyrotoxicosis or acute infections. The atrial rate is between 140 and 220 beats per minute, and there is usually a 1:1 response by the ventricles. In an almost special variety associated with digitalis intoxication, particularly with potassium loss, a 2:1 response is the rule. In patients with coronary heart disease and borderline compensation, congestive failure or angina pectoris may follow the onset of a paroxysm. The rhythm is perfectly regular and the loudness of the heart sounds is monotonously constant, in contrast to ventricular tachycardia, where variability in loudness (especially of the first sound) often is striking. One should try the effect of carotid sinus massage, which either will have no effect whatever or will convert the mechanism abruptly to a normal sinus pattern.

Figure 6 shows that the P waves during the paroxysm are of ectopic origin, but the QRS complexes resemble those seen with normal sinus rhythm. Differential diagnosis includes sinus tachycardia and atrial flutter, especially when flutter occurs with a 2:1 block. In sinus tachycardia the P waves are normal in contour and the rate is usually below 160 beats per minute. Carotid sinus stimulation may be of help in determining whether the disturbance is a paroxysmal atrial tachycardia or atrial flutter with a 2:1 block (figure 7). After carotid sinus stimulation there may be a temporary increase in the atrioventricular block, allowing easy recognition of atrial flutter. When paroxysmal atrial tachycardia follows overdosage of digitalis, the alkaloid should be stopped and potassium chloride given in divided doses totaling 4 to 6 gm. in 24 hours, if the urinary output is adequate. While the oral route is preferable, a slow intravenous drip may be used if necessary.

Some patients have learned to stop their own attacks of paroxysmal supraventricular tachycardia by breath holding, gagging, or self-induced vomiting. Although eyeball pressure can be effective, we advise against it because of possible serious local trauma. Carotid sinus massage should be limited to from 30 to 60 seconds at a session and should not

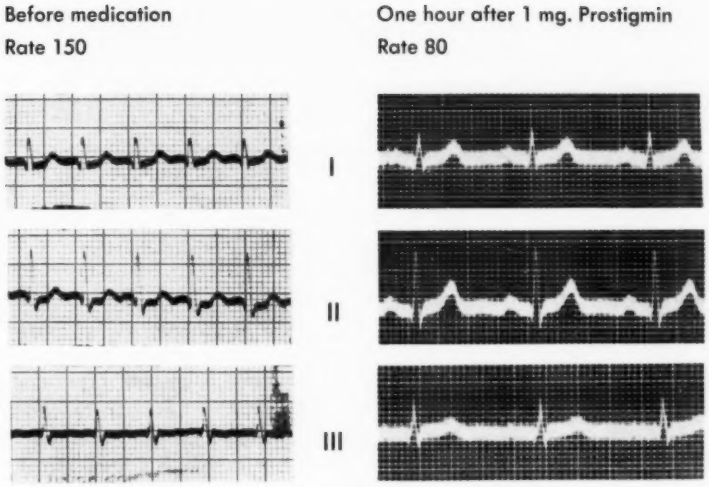

FIGURE 8. Effect of subcutaneous Prostigmin on the heart rate and rhythm of a 22 year old woman with supraventricular tachycardia and no clinical evidence of organic heart disease.

be used on both sides at once. Reflex vagal stimulation by pharmacodynamic means may be produced with systemic arterioconstrictor drugs such as methoxamine hydrochloride (VASOXYL®), phenylephrine hydrochloride (Neo-synephrine) or levarterenol bitartrate (LEVOPHED®). This is a rational and satisfactory drug approach which deserves wider clinical trial. Direct stimulation of the vagal motor effectors can be produced by the use of neostigmine methylsulfate (PROSTIGMIN®), as shown in figure 8. The transition tends to occur gradually, unless carotid sinus pressure is used again after drug action has begun; at this time it is more likely to be effective abruptly if it has been unsuccessful previously. Some serious reactions have been reported with the use of neostigmine,[4] but we have not encountered any difficulty during extensive use of this drug. We avoid using methacholine chloride (MECHOLYL®)[4] because of its severe side actions and the danger of disastrous potentialization if it is employed before or after neostigmine.

If the patient has anginal or congestive heart-failure and has not already had digitalis, he should be given an oral alkaloid promptly or an initial intravenous dose of 0.8 to 1.6 mg. of a drug such as deslanoside (CEDILANID®-D), depending on the degree of urgency. If one cannot be sure that the patient is free of digitalis or that the tachycardia actually is supraventricular in type, quinidine should be employed rather than digitalis. An oral dose of 0.6 gm. quinidine sulfate plus a sedative drug often suffices unless the patient is ill enough to require intravenous quinidine gluconate. Daily maintenance doses of digitalis or quinidine may be needed after successful treatment of the acute attack.

The difference in the configuration of the P waves and QRS complexes in various forms of paroxysmal tachycardia can be demonstrated rarely in a continuous tracing taken from one patient. The remarkably rapid change in the cardiac mechanism from upper nodal to atrial to ventricular tachycardia in one short strip of an electrocardiogram, as shown in figure 9, is very unusual.

Atrial Flutter

Figure 10 shows a type of regular arrhythmia known as atrial flutter. It is characterized by excessively rapid atrial rates of from 250 to 350 beats per minute. Because of the customary presence of some degree of atrioventricular block the ventricular response is slower, but in a definite ratio. It is uncommon in persons without heart disease and is seen especially in patients with mitral stenosis, thyrotoxicosis, recent myocardial infarction, acute infections or surgical or traumatic injury to

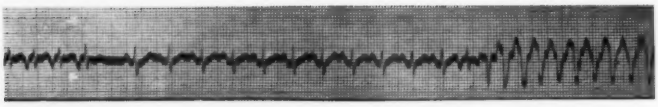

FIGURE 9. Paroxysmal tachycardia. Continuous tracing from one patient, showing spontaneous changes. Note the difference in configuration of the QRS complexes in the nodal and atrial types of supraventricular tachycardia compared with those in the ventricular tachycardia.

the thorax. Palpitation may be the only symptom, or there may be chest pain or symptoms and signs suggesting the advent of congestive heart-failure. One may find a ventricular rate of approximately 150 with a 2:1 block, 100 with a 3:1 block, or 75 with a 4:1 block. Of these, the 2:1 and 4:1 ratios are more common; the 3:1 ratio almost never occurs as a sustained mechanism, but tends to appear when the degree of block is variable. Atrial flutter with a 1:1 response and with ventricular aberration may be confused with ventricular tachycardia. Increase in degree of A-V block in atrial flutter may be induced diagnostically by deliberate carotid sinus stimulation (figure 7), thus enabling one to make the correct diagnosis and use the appropriate drug (i.e., digitalis for atrial flutter or quinidine for ventricular tachycardia). Figure 10 shows the characteristic "saw-toothed" pattern of the regularly occurring flutter waves from a heart with a 4:1 A-V block.

Digitalis is the initial drug of choice, to be given orally or intravenously as indicated. Tolerance to digitalis preparations in patients with atrial flutter often is considerably greater than normal, so that a total of two to three times the usual digitalizing dose may be required eventually to slow the ventricular rate satisfactorily. This drug alone may convert the arrhythmia to atrial fibrillation, and subsequent withdrawal sometimes leads to restoration of normal sinus rhythm. In many cases, on the contrary, the atrial fibrillation persists and quinidine may be used for conversion, if a normal sinus mechanism is desired. Quinidine never should be given in atrial flutter prior to digitalization because of the danger of changing the atrioventricular response to a 1:1 ratio. At rates of 300± beats per minute, this can be fatal in infants or in patients with serious heart disease. A digitalized patient tolerates well five doses of 0.2 gm. oral quinidine sulfate every one to three hours the first day. With repeated examination for conversion of the rhythm or for toxic effects, the dosage may be increased progressively on successive days until a total daily dosage of 4 gm. has been reached. The risk of serious toxicity seldom justifies larger amounts unless facilities for measuring quinidine blood levels are available. Daily maintenance doses of digitalis or quinidine may or may not be needed after restoration of normal rhythm. Some physicians prefer procaine amide hydrochloride to quinidine for conversion attempts in atrial fibrillation.

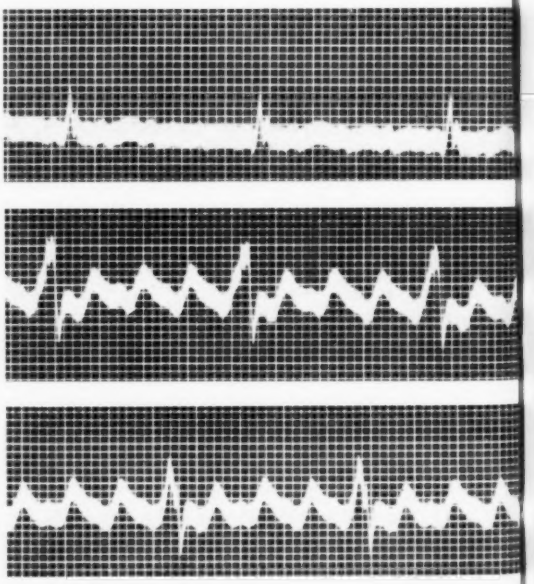

FIGURE 10. Atrial flutter with 4:1 atrioventricular block (leads I, II, III) in a 47 year old man with thyrotoxicosis; atrial rate 264, ventricular rate 66. Note "saw-toothed" pattern of the regular flutter waves, well illustrated here in standard leads II and III.

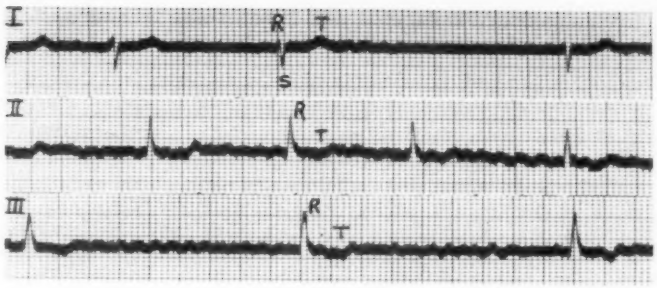

FIGURE 11. Atrial fibrillation in a 34 year old man with no demonstrable organic heart disease. Note the rapid, irregular fibrillatory atrial waves and the slow, irregular ventricular responses.

Atrial Fibrillation

Occurring without preceding atrial flutter, atrial fibrillation (figure 11) is an extremely common and important arrhythmia; it is characterized by very rapid, irregular atrial impulses and totally irregular ventricular responses. Clinically, it customarily is associated with some form of heart disease—rheumatic mitral valvular involvement, coronary artery disease, congenital heart defects, thyrotoxicosis or surgical or traumatic injury to the thoracic viscera. It often is seen in aged patients after they have had other types of surgery. There may be no symptoms with a slow heart and only palpitation when the rate is rapid. The heart sounds reveal an absolutely irregular irregularity. Exercise tends to aggravate this, in contrast to its known tendency to decrease or abolish premature ectopic beats. A radial pulse deficit often exists if the rate is above normal. If the atrial fibrillation is paroxysmal, conversion should be tried. If it is of long standing, the results are not so encouraging or permanent; but in some patients a trial is warranted in order to improve the mechanical efficiency of the heart. Digitalization is the first step and may be adequate in itself. If subsequent addition of the full quinidine regimen as described previously fails, one should be content to keep the rate down within a reasonable range by means of a digitalis preparation. However, if conversion has been achieved, oral daily maintenance quinidine usually is needed to preserve sinus rhythm.

Ventricular Tachycardia

Sequential ventricular premature beats occurring at rates of from 150 to 300 per minute characterize ventricular tachycardia (figure 12). It is associated most often with a recent myocardial infarction, but it can be produced by overdosage of digitalis, quinidine or procaine amide. While it can occur in patients who do not have evident heart disease, there commonly is significant underlying coronary arteriosclerosis or myocardial infarction. The symptoms are those of the associated heart disease, with, perhaps, additional palpitation or pain. Occasionally, there may be Adams-Stokes attacks. The heart rhythm may be very slightly irregular or totally regular. The first heart sound often varies in intensity and quality, and either or both of the two heart sounds may be split widely.[5]

Multiple (often low-frequency) staccato-type sounds recently have been described as being helpful in making a clinical diagnosis of ventricular tachycardia.[6] These physical signs may be helpful in the clinical recognition of ventricular tachycardia in uncommon instances where electrocardiographic discrimination may be difficult, as in (1) atrial flutter with ventricular aberration or in (2) supra-

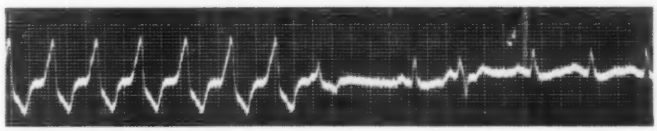

FIGURE 12. Conversion of paroxysmal ventricular tachycardia. Normal sinus rhythm was restored abruptly in this patient by means of the careful use of 0.3 gm. quinidine lactate given by slow intravenous injection with proper electrocardiographic monitoring.[7]

ventricular tachycardia or atrial flutter with bundle-branch block. In such situations, previous electrocardiograms may be especially helpful. Carotid sinus massage produces no slowing in ventricular tachycardia.

Once the diagnosis of ventricular tachycardia has been made, prompt therapy is mandatory. If the attack is due to digitalis intoxication, the drug should be discontinued and potassium chloride should be given in slow intravenous doses of 3 to 6 gm. (40 to 80 mEq.) two or more times daily. If the patient is not in distress, oral quinidine may be used, as described in the treatment of atrial fibrillation, with the administration of hourly doses until conversion occurs. Alternatively, oral procaine amide hydrochloride may be preferred in an initial dose of 1 gm., repeated if necessary in two hours. If no conversion results, 0.5 to 1 gm. doses then can be given under close supervision every four to six hours.

If the patient is seriously ill, one of these drugs should be given intravenously. Quinidine gluconate is available in 10 cc. ampules, containing 0.8 gm. quinidine. The contents of one ampule should be diluted to a 20 cc. volume with isotonic sodium chloride or 5 per cent glucose solution, and the preparation injected at a rate not faster than 1 cc. per minute. The injection should be monitored with a continuous-recording, direct-writing electrocardiograph or, if such is not available, by continuous auscultation over the precordium. This method of administering quinidine has been shown to be safe and effective in our hospital[7] and elsewhere. When a change in rate or rhythm occurs, the injection should be halted and, if conversion has occurred, no further quinidine should be given. If any change occurs in the configuration of the QRS complex, the injection likewise should be stopped. If procaine amide hydrochloride is used, 0.5 to 1 gm. may be given intravenously over a period of 30 minutes, with similar monitoring precautions and frequent determination of the arterial pressure level, to guard against serious hypotension. After conversion to a normal sinus rhythm, oral maintenance therapy, consisting of 0.2 to 0.6 gm. quinidine sulfate, or 0.25 to 0.50 gm. procaine amide hydrochloride, four times daily usually will be required for several days or longer.

Both quinidine and procaine amide are contraindicated if ventricular tachycardia is associated with complete heart-block and Adams-Stokes attacks, as both of the drugs decrease myocardial excitability. Isoproterenol hydrochloride (ISUPREL®), given subcutaneously or sublingually, is then the drug of choice.

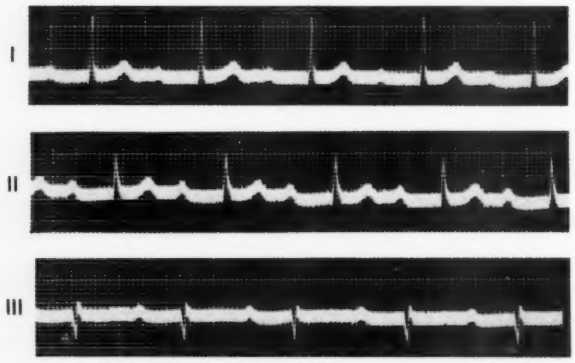

FIGURE 13. First degree atrioventricular block showing P-R interval of 0.40 second in a 73 year old man with arteriosclerotic heart disease.

Atrioventricular Heart-block

There are three different degrees of atrioventricular heart-block, a mechanism in which there is delayed or defective conduction of the impulse from atrium to ventricle.

First degree block—In A-V heart-block of the first degree (figure 13), there is prolongation of the A-V conduction time so that the P-R interval is greater than 0.20 second. The normal P-R interval is between 0.12 and 0.20 second, but longer P-R intervals in apparently healthy individuals have been recorded.[8] Each P wave is followed by a normal ventricular complex. This diagnosis can be made with certainty only by electrocardiography. First degree block is found frequently in acute rheumatic fever in children and is seen occasionally in coronary, luetic or various forms of congenital heart disease. Patients taking digitalis often show this degree of block. The treatment, if any, is that of the underlying disease.

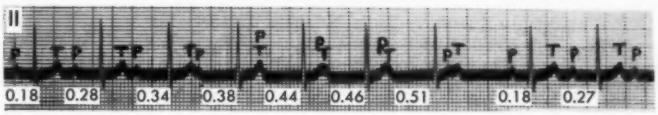

FIGURE 14. Second degree atrioventricular block (Wenckebach type) in a 21 year old man with acute rheumatic fever and rheumatic heart disease, not taking digitalis. Note the progressive lengthening of the P-R interval from 0.18 to 0.51 second before failure of ventricular response to the sino-atrial impulse occurs. After the pause, the next P-R interval has returned to a normal 0.18 second.

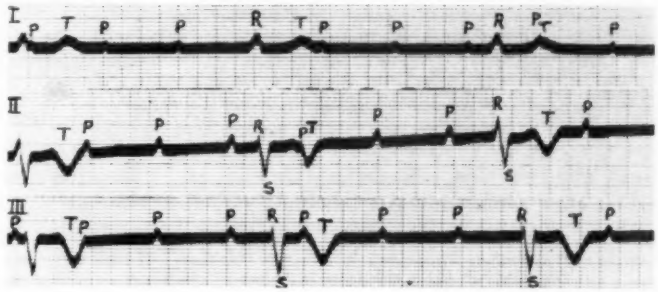

FIGURE 15. Third degree (complete) atrioventricular block in a 63 year old man with coronary atherosclerosis and syncopal attacks, not taking digitalis or quinidine.

Second degree block—Not all of the atrial impulses are followed by ventricular contractions in second degree atrioventricular block. There may be a variable block or a fixed ratio; e.g., 2:1 or 3:1. Dropped beats can be recognized periodically on auscultation. The Wenckebach phenomenon is a form of variable second degree block (figure 14). The P-R interval progressively increases until, eventually, there is no ventricular response to the atrial impulse. This type commonly is associated with digitalis intoxication. After the dropped beat, the cycle repeats itself, as A-V conduction is re-established. Second degree A-V block may be seen also in various forms of acquired heart disease. Again the treatment is that of the basic disease process or management of the digitalis intoxication, if present.

Third degree or complete heart-block—As shown in figure 15, no supraventricular impulses discharge the atrioventricular node when this condition is present. If an idioventricular rhythm is not produced then by a ventricular pacemaker, cardiac standstill with an Adams-Stokes attack occurs. There is complete atrioventricular dissociation; i.e., the QRS complexes bear no constant time relationship to the P waves. In general, the atrial rate is from 70 to 80 beats per minute, while the ventricular rate is from 30 to 40. The QRS complexes in complete heart-block are normal in configuration when the pacemaker controlling the ventricles is in the atrioventricular junctional tissues. If the ventricular pacemaker is in an ectopic focus in the ventricle or in one of the bundle branches, the QRS

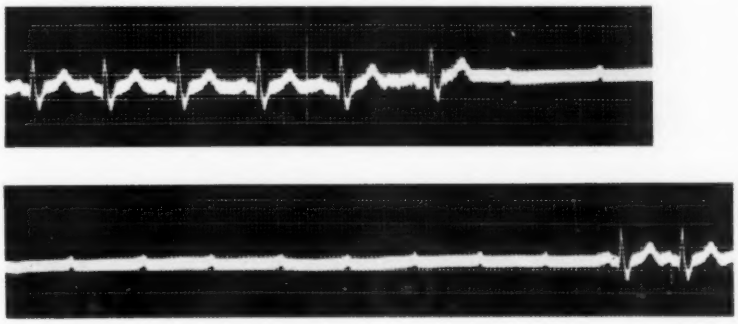

FIGURE 16. Sudden complete atrioventricular block and ventricular arrest in a 63 year old man ill with probable first attack of acute rheumatic fever. He had had many spontaneous Adams-Stokes attacks with convulsions. Other tracings confirmed the tracings of incomplete right bundle-branch block also.

complexes are slurred, widened or notched. Figure 16 is a continuous-strip record of the sudden onset of complete A-V block, with resultant ventricular arrest and, finally, resumption of a normal sinus rhythm.

Coronary atherosclerosis is the chief cause of complete heart-block. Several reports are available on congenital complete atrioventricular block.[9-11] Various forms of reflex vagal stimulation have produced partial and complete heart-block. Some of the infectious diseases, especially syphilis and diphtheria, occasionally have been responsible. Recently, an article cited Adams-Stokes attacks in a patient with elevated serum potassium in a clinical condition that was apparently "pure" hypoaldosteronism.[12]

Treatment of third degree heart-block is necessary when it is associated with symptoms, especially dizziness or Adams-Stokes attacks.[13] If digitalis, quinidine or a narcotic is responsible for recurrent attacks, the drug should be withdrawn. When there is cardiac standstill, a sharp blow with the hand or fist on the chest wall over the heart may restore ventricular beats. Epinephrine hydrochloride in subcutaneous or intramuscular doses of 0.3 to 1 cc. of the standard 1:1000 solution is acceptable as an emergency drug in recurrent syncopal attacks, but 10 to 20 mg. doses of isoproterenol hydrochloride sublingually are preferable. Subsequent subcutaneous doses may be used every one to six hours as needed to prevent further attacks shortly after an emergency episode. If necessary, an intravenous infusion of 1 mg. in 200 cc. 5 per cent glucose may be given at 10 to 20 drops per minute for urgent situations. Isoproterenol also has been reported to terminate syncopal attacks due to ventricular tachycardia or fibrillation, as well as those resulting from ventricular standstill.[14,15] Bellet, Wasserman and Brody[16] have used intravenous molar sodium lactate to restore ventricular rhythm in acute circumstances. Zoll's artificial external electric pacemaker[2] is especially useful and always potentially lifesaving in prolonged Adams-Stokes attacks. Both quinidine and procaine amide are contraindicated. However, digitalis should be used if there is associated congestive heart-failure and if the block has not been caused by a digitalis preparation. For maintenance of protection 10 to 20 mg. oral isoproterenol hydrochloride, 15 to 30 mg. ephedrine sulfate or 20 to 60 mg. hydroxyamphetamine hydrobromide (PAREDRINE®) three or four times daily should be satisfactory.

Ventricular Fibrillation

Usually a fatal, terminal arrhythmia, ventricular fibrillation (figure 17) is characterized by rapid, chaotic, totally ineffectual ventricular twitchings. It may occur without any warning in patients having recent myocardial infarction or it may develop as a sequela of ventricular tachycardia; it can be produced by overdosage of digitalis or quinidine. Paroxysmal ventricular fibrillation has been reported rarely in the absence of demonstrable evidence of heart disease.[17,18]

In recent years, especially in thoracic surgical procedures involving repair of congeni-

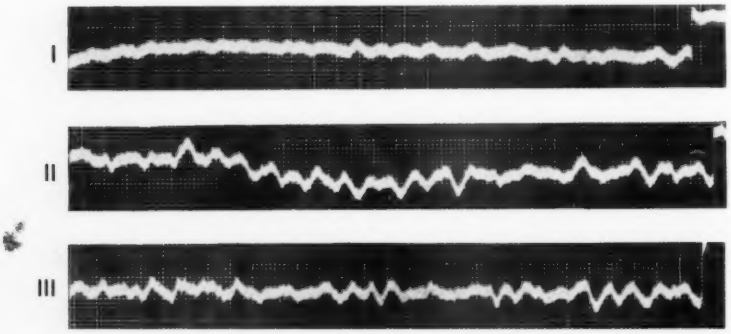

FIGURE 17. Ventricular fibrillation in a 45 year old man who had a sudden fatal coronary thrombosis while having a gastrointestinal x-ray examination in the hospital. Death occurred within three minutes after lead III had been recorded. There was no history of previous cardiac symptoms.

t l heart defects, electric defibrillation has l en very effective in restoring a normal car- iac mechanism. This has been especially true when the patient has had preoperative hypothermic preparation. One patient who underwent closure of an atrial septal defect under hypothermia at the State University of Iowa Hospitals was restored successfully after having had ventricular fibrillation intermittently for two hours in the operating room. More than a year later, the patient had no demonstrable neurologic or other systemic defect. An electric defibrillator should be available in all hospitals as emergency equipment.

Summary

Proper management of the more common cardiac arrhythmias requires accurate diagnosis based on the skillful use and interpretation of the history, physical examination and electrocardiographic tracings. Appropriate drug therapy then can be instituted when needed. The newer drugs and effective biophysical methods of treatment, such as the external cardiac pacemaker and the electric defibrillator, offer us helpful additional means for treating arrhythmias, as well as for investigating further the mechanisms involved in their production. It is gratifying indeed that these potentially frightening disorders can be treated successfully so often.

ACKNOWLEDGMENT

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Electrolytes and Nutrition

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IT is significant that a word for salt was not a part of the language of nomadic people. It would appear that salt was not known in the households of the roaming tribes, and that the need for salt and the use of the word "salt" arose concomitantly with the transfer from a wandering to a settled existence. Of course, this necessitated preservation of meat and game at a time when there was no refrigeration; hence, the use of salt probably is an acquired taste. Nevertheless, many of us believe that salt is an essential constituent of our daily diet. To what extent is this true?

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The studies of Cuttino, Paris and Rosenthal[1] show clearly that growing animals will not gain weight at a normal rate unless both sodium and chloride are supplied in the diet. Either sodium or chloride alone proves inadequate. It is obvious, therefore, that in the case of the immature animal, sodium and chloride are necessary for normal growth. Does this need persist once growth has been completed and the adult phase has been reached? Apparently not, provided renal conservation of sodium and chloride is perfect and extra renal losses of these electrolytes do not occur. Therefore, existing in the body are very precise homeostatic mechanisms for maintenance of body sodium, chloride and water stores within the very narrow limits which characterize health. I need only point out that our dietary intake of these constituents varies from day to day, yet our body weight alters but little. One day we may eat preserved foods such as ham, which has a large content of sodium, and drink excessive volumes of water; another day we may be on a salad regimen, with limited fluid intake. Yet our body weight remains constant.

Sodium Homeostasis

What are the mechanisms for maintaining body sodium stores constant in the face of varying intake? Certainly the kidney plays an all-important role. The bulk of filtered sodium and chloride is reabsorbed in the proximal tubules, and adjustments in accord with the body needs are made in the distal tubules. These are controlled in a rather precise fashion by adrenocortical steroids and, presumably, primarily by aldosterone. However, the kidney does have an inherent ability to reabsorb filtered sodium not conditioned by adrenocortical steroids; this is evidenced by the fact that the patient with Addison's disease still does not lose that amount of salt which escapes reabsorption in the proximal tubules.

There are some rather informative nutritional experiments in rats which emphasize the role of the adrenal cortex in this economy of body electrolytes. For example, if a rat is placed on a diet which is totally devoid of sodium, within a matter of two or three days its urine becomes sodium-free.[2] If the animal is then sacrificed and the adrenal cortices are examined, they are found to be increased in size, and histologic evidences of an increased output of steroids are present. Conversely, if such an animal is salt-loaded, the adrenal cortex atrophies or, rather, decreases in size. Presumably, these are reflections of an increased and decreased secretion of aldosterone respectively. Interestingly enough, this homeostatic mechanism does not appear to be under any significant degree of control by the anterior pituitary. Thus, the hypophysectomized animal responds to changes in sodium loading just as well as does the normal animal;[3] this observation is in contrast to other functions of the adrenal cortex.

Patients who have tumors of the anterior pituitary, or anterior pituitary insufficiency from other causes, are not necessarily salt wasters. However, although the anterior pituitary does not appear to play any significant role in regulating aldosterone excretion, there is evidence that there are higher centers which control its output. The exact location of the center or centers has not been identified, but aldosterone excretion does decrease following decapitation.[4] Such centers may be the site of electrolyte disturbances such as those present in cerebral salt wasters.[5]

During periods of sodium deprivation, most patients react in exactly the same way as does the normal or the hypophysectomized rat. On a low sodium regimen, such as a rice diet or a low sodium milk formula, the urine becomes sodium-free in a matter of a few days, provided the adrenal cortices are intact.[6] The excretion of sodium at other sites also can be altered by variations in adrenocortical activity. This is true, for example, of sweat, and it can be demonstrated to occur in the gastrointestinal tract by means of cation exchange resins.

Low Sodium Syndromes

What are the effects of circumventing or destroying these conservation mechanisms? Hyponatremia or a low sodium syndrome results. This is the salt-depletion type of low sodium syndrome, and it must be differentiated from four other types.[7] Such sodium depletion may occur as a consequence of destruction of the adrenal cortices, as in Addison's disease, or following adrenalectomy. This loss of sodium is followed by circulatory collapse which can be as profound as that which follows hemorrhage, trauma or burns.

The sequence of events may be outlined as follows: With loss of sodium, extracellular hypotonicity develops and causes a shift of water from the extracellular fluid into cells; the cells become swollen, and the extracellular fluid decreases in volume. It is particularly significant that there is a preponderant loss of water from plasma; the probable reason for this is that as sodium is removed from the extracellular fluid, albumin also leaves the plasma and is presumably segregated somewhere in the tissues. Since each gram of albumin holds some 20 cc. of water in the plasma, the plasma volume declines to an extent greater than the decline in the extracellular fluid as a whole. The viscosity of the blood rises and the circulation slows. The venous return to the heart diminishes and the cardiac output and blood pressure fall.[8-10]

This type of low salt syndrome or salt depletion also can be produced inadvertently in patients by intubation of the gastrointestinal tract, employing 5 per cent glucose or tap water in the lavage fluid. Under these circumstances, sodium passes into the lavage fluid and is lost from the body.

There are other causes of low salt syndrome of the depletion type. For example, in mucoviscidosis large amounts of sodium and chloride may be lost in the sweat, which may cause circulatory collapse. The cerebral salt wasters mentioned earlier may also go into circulatory collapse as a consequence of sodium depletion. If the patient survives the cerebral injury, or whatever the lesion may be, he regains the ability to conserve sodium. Rarely, we may find patients with renal disease who are true sodium wasters and in whom, therefore, a low sodium syndrome of the depletion type may develop. Sodium depletion also may occur in patients who have been overtreated with mercurial diuretics or who are receiving cation exchange resins, and in patients with diarrhea, vomiting and draining fistulas or surfaces. The same physiologic changes may follow segregation of extracellular electrolyte in subcutaneous pools of glucose in water administered as a hypodermoclysis.

The second form of low sodium syndrome is that resulting from chronic hypo-osmolarity.[7] Chronic disease and malnutrition may result in a loss of cellular constituents, including units that are osmotically active. The resultant hypo-osmolarity is reflected in lowered sodium levels in the fluid outside the cells. Although first described in 1938 by Winkler and Crankshaw[11] in relation to patients with pulmonary tuberculosis and other forms of lung disease, this type of low sodium concentration may develop in any patient who is chronically ill.

Though all of these categories of hyponatremia are instances of depletion, only the first group cited can be called acute. The others might be regarded as a type of chronic depletion. Only the first category is associated with circulatory collapse; the second type is not, perhaps because the loss is not as great and because it occurs over a longer period of time.

A third type of low sodium syndrome is that encountered following the administration of an excess of water.[7] In this form, the total sodium stores of the body remain intact. This syndrome may be encountered in the patient with anuria to whom a solution of 5 per cent glucose in water is administered in an attempt to produce a flow of urine. If this does not occur, the excess of water is, of course, retained, and the total body sodium stores become diluted. This is obviously a form of water intoxication; it also may be encountered postoperatively as a result of the limited ability of such patients to excrete water. Finally, it can be produced experimentally by the continued administration of an antidiuretic hormone and water.

Sodium levels also may be low as a result of an excess of lipid in the serum, as in diabetic acidosis or coma and nephrosis.[12] This is an artifact, since the concentration of sodium in the water of serum is normal and is without any particular physiologic significance other than the fact that the patient is ill.

The fifth category of low sodium syndrome is called the new steady state, implying that the regulators of the concentration, the distribution and the volume of body fluids have been set at new levels.[7] It is not associated with a deficit of sodium, but is characterized rather by an excess of both sodium and water. Edema and hyponatremia coexist. This is an ominous development in the course of an illness. In my experience, about one-half of such patients have died in the course of hospitalization. The condition is seen most commonly in intractable congestive heart-failure, in far-advanced renal disease, in patients with cirrhosis, and in toxemia of pregnancy.

Origins and Significance of Hypernatremia

What happens when the concentrations of sodium rise? The intravenous administration of excessive amounts of hypertonic saline into animals produces death as a result of respiratory failure at a time when the circulation is very well maintained.[13] At that point, the pulse is still full and bounding and the blood pressure is normal, yet the animal dies because of respiratory failure. The pathophysi-

logy is simple: Since sodium is largely an extracellular ion, the introduction of hypertonic solutions produces hypertonicity of the extracellular fluid and dehydrates the cells. The cells which show the first manifestations of major alterations in function are those which are most sensitive to dehydration. These are the cells of the nervous system and of the respiratory center in particular.

The same degree of hypernatremia can be achieved even without infusing hypertonic saline; failure to give sufficient water will produce the same result. As a matter of fact, Broch[14] described a series of such patients who had strokes and who did not receive their daily quota of water. He followed their levels of sodium and noted that they died of respiratory failure because of the hypernatremia produced by water deprivation.

An excess of sodium with or without hypernatremia can be produced in perfectly normal subjects merely by overloading the excretory capacity, i.e., by infusing saline or by administering sodium chloride at a rate in excess of the excretory ability of the kidneys. Far more often, however, an excess of sodium results from a diminished renal excretory capacity, as in congestive heart-failure, cirrhosis, renal failure, toxemia of pregnancy, or any illness characterized by secondary aldosteronism.

Potassium

Potassium is an essential component of body cells. Studies in animals have established that potassium is a necessary component of the intake of a growing animal.[15] If it is not supplied in optimal amounts, the animal does not gain weight at a normal rate. Potassium also must be available in the daily diet in health and in disease if depletion is to be avoided.

Responses to and manifestations of potassium depletion—The mechanisms for potassium homeostasis do not appear to be as effective as in the case of sodium, at least in the ill or the stressed person. Thus, in patients deprived of this constituent, day after day the urine continues to contain significant amounts of potassium. Under these circumstances, the ability of the kidney to conserve potassium is not as precise as it is in the case of sodium. This is probably related, in part at least, to the associated discharge of adrenocortical steroids which facilitate the renal output of potassium. If the element of stress can be removed, the experimental animal and the human begin to conserve this electrolyte quite effectively during periods of deprivation.[2]

The clinical manifestations of hypopotassemia are familiar:[16-18] With low levels in the extracellular fluid, sensory disturbances may occur, such as numbness, tingling and paresthesia, motor weakness or actual paralysis of the voluntary musculature, and paralytic ileus. The electrocardiogram reveals lowering of the T waves, prolongation of the Q-T interval, and disturbances of rhythm.

Deficits of potassium within the cellular matrix may result in destruction of the cells. Such losses of potassium are accompanied by necrosis of the skeletal and the cardiac musculature. It is quite probable that many cells lose their functional efficiency in cases of potassium depletion long before these gross morphologic manifestations are evident. Such depletion of potassium is a very common feature of any situation in which intake of food is cut off, as in bulbar paralysis, in the infant who is neglected, or in the adult who cannot eat because of carcinoma of the esophagus. In all these instances, patients are stressed, and they continue secreting urine which contains potassium. The net effect is cellular depletion.

Effects of excessive potassium—An excess of potassium in the extracellular fluid produces cardiotoxicity and the cardiac standstill following a fairly predictable series of changes in the electrocardiogram.

There is no evidence that an excess of potassium within cells is harmful. As a matter of fact, this is probably a safety mechanism for the maintenance of normal levels of potassium in the extracellular fluid. When levels rise in the extracellular fluid or when the organism takes in more potassium than it can excrete, the potassium can be stored temporarily within the cells.

Diabetic Acidosis Coma

Before concluding this discussion of electrolytes and nutrition, I would like to review the

changes in the clinical entity of diabetic acidosis coma, in which there are gross disturbances of nutrition, water and electrolytes.[19-21] Patients with this condition have a frequent history of vomiting. This interferes with an intake of water, electrolytes and foodstuffs and is accompanied by a loss in the body's own stores of water, sodium, chloride and potassium. Since the formed stool normally contains but a small amount of sodium, and since most patients with acidosis and coma do not have diarrhea, one would not expect an external loss via this route. However, some segregation of water and of electrolytes will occur with dilatation of the bowel or stomach, which may develop.

Ordinarily, one would expect the renal conservation response to minimize the excretion of sodium, but the diabetic patient is undergoing an osmotic diuresis, and the glycosuria interferes with the reabsorption of filtered sodium. The net effects of this loss of sodium in excess of water are a hyponatremia, a salt depletion type of low sodium syndrome, and circulatory collapse. These are common features of far-advanced acidosis and coma.

Insofar as the potassium metabolism in diabetic acidosis coma is concerned, this element is lost from the cells in several ways. Thus, when liver glycogen is released, potassium is set free at the same time; this occurs because glycogen which is formed in the liver is laid down with a fixed modicum of potassium. Also, with starvation, cell breakdown and loss of cell protein, potassium is lost. Furthermore, with dehydration, the cells release potassium, so that the dehydration in the extracellular fluid may be mitigated. Finally, the decrease in the rate of glycolysis in acidosis and coma permits a pouring out of cell potassium. The net effect of all these processes is a loss of potassium from cells to the extracellular fluid and to the exterior by way of the urine and in vomitus.

This trend of potassium loss from cells is reversed with the administration of insulin. Glycogen is laid down in the liver with the potassium; the freed nitrogen which can be salvaged is reutilized and reincorporated into cell protein; the dehydration is corrected; as water moves back into the cells, potassium goes with it; and finally, as normal rates of glycolysis are re-established, the concentrations of potassium in cells are restored.

These movements of potassium into cells lower the concentrations of potassium. At the same time, urinary losses of this element continue; if the patient is being treated with fluids that have no potassium, the extracellular fluid is expanded and hypokalemia appears. Hence, administration of potassium to these patients during the third or fourth hour following the beginning of recovery is standard practice.

Perspectives on Laboratory Findings

In the course of any discussion of electrolytes, one might be left with the feeling that all decisions are easily reached because the laboratory provides the answers. This is not usually so. Decisions are to be based on a knowledge of the fundamental features of the disorder, on the particular history obtained, and on common sense, with the laboratory usually playing a substantiating role only. However, a diagnosis of sodium or potassium depletion is to be made on the basis of history, not on the basis of the laboratory findings. If the history indicates the patient has been vomiting and is in circulatory collapse, it is probable that sodium deficits are present even though sodium concentrations are normal. This finding merely means that sodium and water have been lost in the same proportions in which they exist in the body. Similarly if the patient has not eaten for two weeks and has continued to secrete urine, he has potassium depletion even though potassium levels are normal.

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Postgraduate Clinical NOTES

94. ALKALOSIS

Alkalosis results from the loss of gastric hydrochloric acid. There are few bodily compensations for this disorder. There appears to be little respiratory compensation. The principal relief is offered by the continued excretion of an alkaline urine, and yet this is compromised by the retention of sodium bicarbonate that occurs after trauma. Injury of itself therefore makes the patient much more vulnerable to alkalosis, in part by the tendency to resorb sodium bicarbonate from the glomerular filtrate (an aldosteronelike effect) and in part by the tendency to develop differential potassium loss (that is, potassium loss at a high K:N ratio). Potassium deficit also interferes with the excretion of an alkaline urine. Trauma and potassium deficit therefore combine to make the urine acid despite extracellular alkalosis. The worsened alkalosis of trauma joins with potassium loss in lowering the plasma potassium concentration when surgery is superimposed on loss of hydrochloric acid.

Francis D. Moore, Common patterns of water and electrolyte changes in injury, surgery and disease, *New England Journal of Medicine*, February 6, 1958, pp. 277-285

Surgical Reconstruction for Arterial Occlusive Disease

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To relieve constant, burning, sleep-robbing pain; to see sickly pallor change to living pink; to watch faltering, painful steps at 50 paces lengthen and then change to free painless ones, as many as the will desires—all this brings satisfaction rarely matched in the practice of medicine. Such are the frequent rewards of restoring blood flow in a major blood channel to a leg.

We can now add obstruction due to segmental arteriosclerotic disease to obstruction due to injury, neoplasm, embolism, arteriovenous fistula or congenital anomaly in that it is often amenable to correction surgically. Success depends on restoring adequate circulation before the organ that the vessel supplies is seriously damaged. In arteriosclerotic disease the possibility and extent of present improvement as well as the duration of benefit depend not only on the technical success of restoration of flow by endarterectomy or grafting but also on the presence and persistence of open channels above and below the level of primary occlusion.

Pathology

In traumatic thrombosis of an artery the damage to the arterial wall extends beyond the region of grossly visible disease. Neoplastic invasion of a major artery no longer precludes resection, but surgical reconstruction is often futile because of the ancillary extensiveness of the lesion. The degenerative changes of arteriosclerosis affect chiefly the intima and subintima. Atheromatous and calcific changes narrow the lumen and invite final thrombotic occlusion. Occasionally the tunica media degenerates, with resultant dilatation and formation of aneurysm. More often the wall is intact and the sclerotic and thrombotic lesions of the lumen, intima and subintima may be removed and an intact wall will re-

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pain. Atherosclerosis is a systemic disorder affecting many vessels and organs. However, lesions producing significant symptoms may be confined for years to one organ or to relatively isolated segments of major vessels.

Clinical Manifestations

The cardinal symptom of ischemia of an extremity is intermittent claudication or pain in affected muscles on exercise and prompt relief with rest. If a patient can walk briskly for six or eight blocks without discomfort, one may safely conclude that serious arterial insufficiency does not exist. Pallor on elevation is the most delicate sign of arterial insufficiency. Delayed return of color on dependency is corroborative. With severe ischemia there is insufficient blood to supply the tissues at rest and the leg is painful even at rest. Gangrene is imminent.

Diagnosis

The foregoing symptoms and signs establish the diagnosis of arterial insufficiency. The determination of the presence and quality of arterial pulsations localizes the level of occlusion. Oscillometry confirms this localization and supplies additional information. By these simple clinical means one may accurately determine points of major occlusion within a few inches.

Prior to surgical reconstruction it is essential to have more specific information as to the severity and distribution of occlusive processes. Arteriography provides valuable information relative to (1) the severity and extent of the primary occlusion, (2) patency of major vessels below the primary occlusion, and (3) the presence of unsuspected occlusive lesions proximal to the point of major occlusion or in the contralateral extremity.

I have gradually arrived at the conviction that in any case of arterial insufficiency involving one lower extremity a complete roentgenographic mapping of the lower abdominal aorta and all major arteries as far as the lower third of both legs is indicated. The primary examination involves percutaneous translumbar penetration of the aorta. A local anesthetic is employed, and large doses of premedication are given. Thirty milliliters of 50 per cent HYPAQUE® is injected as rapidly as possible through a large-bore No. 18 French needle. A roentgenogram of the abdomen is made as the injection is being completed. A picture of the thighs is taken with a portable machine a few seconds later, the interval depending on the suspected severity of the occlusion. If refilling does not occur below the occlusion, it may be necessary to explore the distal artery to determine its patency. If the arteries of the leg have not been visualized previously, a popliteal arteriogram is made at operation.

One of the most difficult aspects of arterial surgery is development of judgment in deciding when grafting should or should not be attempted in cases in which there is limited distal runoff. The popliteal film is important in determining the adequacy of the low runoff and may prevent fruitless and damaging grafting into a popliteal artery whose major branches are severely stenosed. Complete roentgenographic mapping also may reveal unsuspected segments of proximal or contralateral stenosis which would necessitate more extensive surgical procedures to provide satisfactory and lasting benefits (figures 1, 2 and 3). I suspect that many late failures of grafts are due to progression of stenotic lesions proximal to the grafts.

Treatment

Reconstruction of an occluded vascular tree may be effected by removal of the obstructing elements from the lumen of the vessel (thrombo-endarterectomy), removal of extrinsic scar or tumor (unbridling or decompression), insertion of a new vessel to replace or supplement existing vessels, or some combination of these procedures.

Thrombo-endarterectomy—Arteriosclerosis produces proliferative degeneration of the intimal and subintimal tissues. The lumen of the vessel narrows, and thrombosis ultimately occludes the narrowed, irregular lumen completely. In such cases a plane of cleavage is readily entered which permits removal of all the occluding elements; this leaves some of the tunica media and adventitia to form a wall for the vessel. This wall is rough, and after ex-

FIGURE 1. A 68 year old man had recent severe manifestations of arterial insufficiency in the left leg. Old arterial insufficiency involved the right leg, but this had not produced symptoms recently. Pulses were absent on left side. Right femoral pulse was felt, but pulses were absent below this level on the right. Arteriogram revealed extensive occlusion on left, *severe stenosis of right common iliac artery*, and complete occlusion of right superficial femoral artery. A graft was successfully inserted from the aorta to both of the popliteal arteries.

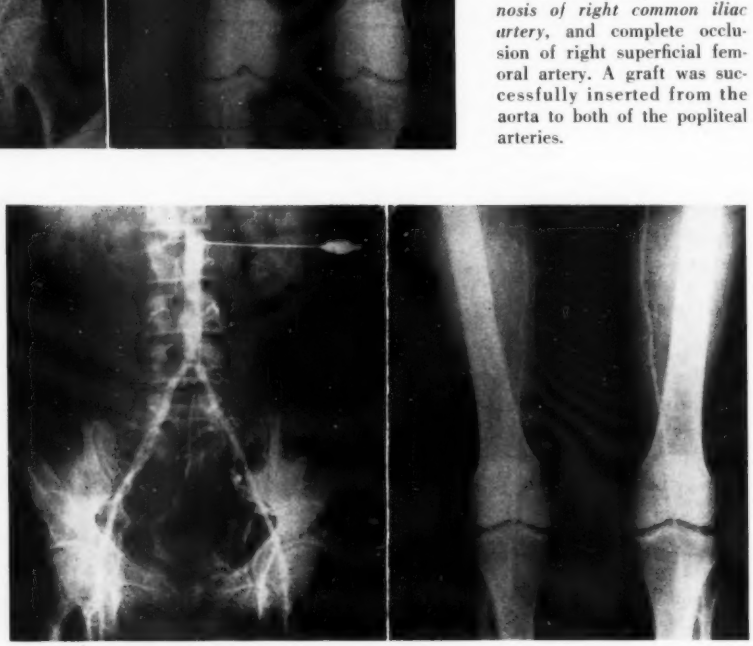

FIGURE 2. A 54 year old white man had progressive claudication in calves and hips for two years. Right femoral pulse was strong. All other pulses were absent. Arteriogram demonstrated complete occlusion of left common iliac artery and right superficial femoral artery, and *severe stenosis of right common iliac artery*. Circulation was restored by performance of endarterectomy above and insertion of right femoral bypass graft.

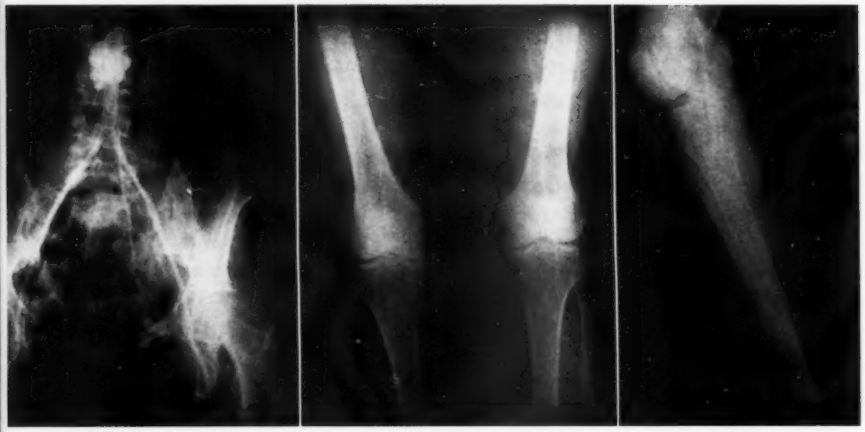

FIGURE 3. A 52 year old woman had severe manifestations of arterial insufficiency in the right leg, with signs of moderate arterial insufficiency in the left leg but no symptoms. Arteriogram showed slight narrowing of left common iliac artery and occlusion of right *and left* superficial femoral arteries. Bilateral bypass grafts were inserted, restoring blood flow. Popliteal runoff was satisfactory; right popliteal arteriogram was made at operation.

tensive procedures of this type anticoagulant therapy is necessary to prevent renewed thrombosis. Often a few days elapse before satisfactory pulsatile distal blood flow is established. Care must be exercised not to leave a loose intimal flap at the lower end of the dissection, as it may dissect up and occlude the vessel.

Three technics are currently used. The technic introduced by Raboul, as reported by Bazy and co-workers,[1] consists in making a longitudinal incision in the wall of the vessel throughout the involved segment. This facilitates accurate thrombo-endarterectomy. The lone arterial incision may be sutured over a temporary catheter stent to minimize narrowing. Extensive disease requires long cutaneous and arterial incisions, and the reparative suture may compromise the lumen of the vessel. For short defects in large vessels the technic is simple and reliable, and it is particularly useful for lesions in the lower abdominal aorta.

Julian and co-workers[2] introduced the technic of transection of the vessel just below the involved segment. Endarterectomy is effected by peeling back the outer coat of tunica media and adventitia while the inner occlusive material is removed. This technic is particularly useful in short occluded segments of a medium-sized or small artery.

The technic currently employed by those most active in the field is the Wylie[3] modification of the original dos Santos[4] method. Short longitudinal or transverse incisions are made just beyond either end of the involved segment, and an intraluminal wire loop stripper is used for debriding. Wylie[3] and Cannon and Barker[5] reported good results with this technic even for extensive lesions in the popliteal and femoral vessels.

Most surgeons have abandoned extensive endarterectomy, as the technic is difficult and the incidence of early reocclusion has been distressingly high. It may be that the incidence of late occlusion will be lower than it is with arterial homografts. The necessity of postoperative anticoagulant therapy and the delay in appearance of a distal pulse indicate that the margin of safety is small for extensive lesions. Endarterectomy is useful as an adjunct to grafting, to clear the vessel proximal to the graft area. It is also useful for short defects and may be employed in small as well as large vessels.

Grafting—Originally the grafts employed for replacement of necessarily limited segments of involved vessels were biologic material, either autogenous vein or homologous artery. Early thrombosis occurred often after use of venous grafts,[6] and late thrombosis has been reported frequently with use of small-caliber arterial homografts.[7-9] When small vessels are involved, a bypass graft is preferable to a replacement graft, because stenosis occurs less frequently at points of anastomosis and, if the bypass graft should become occluded, this is less serious. Kunlin and co-workers,[10] Cockett,[11] Linton and Menendez,[12] and Crawford and DeBakey[13] emphasized the advantages of leaving the host vessels undisturbed and placing the graft as a lateral bypass. Arterial homografts, particularly of smaller vessels, are often difficult to obtain, require meticulous preparation and preservation, and are not completely reliable. In some instances there is an apparent host reaction which gradually leads to thrombotic occlusion of the graft.[9] For these reasons, a vigorous search has continued for suitable synthetic substitutes.

Histologic study of homografts indicates that all graft tissue except the inert elastic fibers promptly degenerates.[14] A new intima forms from fibrin which is laid down and in which apparently leukocytes assume the characteristics of connective tissue. Although the inner wall of the graft remains impermeable to blood, connective tissue from the host infiltrates the adventitia and the outer layers of the tunica media to strengthen the graft wall.

For synthetic structures to serve as suitable blood channels they must: (1) not precipitate a severe inflammatory or late neoplastic reaction, (2) retain adequate strength of the wall, (3) have a low or absent incidence of thrombosis, (4) have adequate flexibility to prevent kinking and to bend with the part involved, and (5) be sufficiently permeable to permit ingrowth of host connective tissue. It was once assumed that some permeability of the entire wall was necessary, but it is probable that permeability of the inner surface of

the graft is unnecessary and indeed undesirable in that it permits leakage of blood when the channel is first opened.

In the abdominal or thoracic aorta the vessel is so large and the question of flexibility so unimportant that many synthetic grafts as well as homografts have proved satisfactory. TEFLON® and DACRON® are well tolerated and retain their tensile strength. Untreated nylon rapidly loses tensile strength,[15] but when pretreated with formic acid and silicone it retains its initial strength for long periods.[16] In small vessels, particularly in the extremity, all inflexible plastic material has proved unsatisfactory because of kinking and buckling. Development of the crimped tube by Edwards and Tapp[17] is the most significant advance in the use of synthetic tubes in the peripheral arteries. These tubes are flexible, do not buckle, and will not kink when placed across a flexion crease.

Plastic grafts have the inestimable advantages of being readily available in any quantity or length and of being readily sterilized. In my experience over a period of one year the Edwards-Tapp tube has proved as satisfactory initially as have homografts and I have not seen a single case of late thrombosis.

Autogenous venous grafts are satisfactory for peripheral vessels, but obtaining them adds time and trauma to an operation and the caliber and length are limited. The incidence of successful venous grafts has not been very high.[2,6]

I prefer to use the Edwards-Tapp nylon tube whenever possible. At the aortic bifurcation level the aortic graft with crimped lower limbs is used. For grafts at the iliac level the 3/8 in. tube is used, and at the femoral and popliteal levels the 5/16 in. tube is preferred. Thrombosis is likely to occur if smaller tubes are employed. End to side anastomosis, particularly distally, reduces the need for a *branching* graft, but at times such a graft is highly desirable and this lack constitutes a major deficiency of all types of artificial grafts currently available.

I began using a number of arterial homografts, and then a few knitted nylon grafts of the Sanger[18] type in the abdominal aorta. I have not used venous grafts. In some cases endarterectomy has been the primary procedure, but more frequently it has been em-

TABLE 1

SURGICAL RECONSTRUCTION FOR ARTERIAL DISEASE; JULY 1955 TO MARCH 1957

LOCATION	CASES	PROCEDURES	RESULTS			
			Circulation restored	*Excellent*	*Improved*	*Amputation*
Aorto-iliac						
Endarterectomy	5	6*	5	4		1†
Grafting	12	20	18	8	3	1†
Femoropopliteal						
Embolectomy	2	2	2	2		
Grafting	10	12	8	7	1	2
Combined high and low occlusions	6	15‡	15	4	2	
Renal artery	3	2§	2	2		
Carotid artery	3	3‖	3	2		
Thoracic aorta	2	2	2	2		
TOTAL	43	62	55	31	6	3

*One an embolectomy.

†Same extremity.

‡Two endarterectomies; others grafts.

§One nephrectomy.

‖One death.

p oyed as an adjunct to grafting. Most of my grafts, and almost all of them in the past year, have been Edwards-Tapp tubes.

Clinical Experience

From July 1955, when I returned from military duty, to March 1957, I performed 62 procedures on 43 patients with arterial occlusion or stenosis. In two cases of aortic coarctation and two cases of juvenile renal arterial stricture the lesions were apparently congenital. Embolism caused occlusion of the aortic bifurcation in one case and of the femoral bifurcation in two. One case of stricture of the internal carotid artery was caused by periarteritis many years before, and one case of occlusion of the common carotid artery resulted from injury. One case each of stricture of the internal carotid artery and of the renal artery, and all cases of occlusion of the aorta and iliac, femoral and popliteal vessels were secondary to arteriosclerosis. In two of these, aortic occlusion was associated with aneurysmal formation. This experience is summarized in table 1.

Most of the procedures involved restoration of the blood flow to the lower extremities. In two cases of homografting at the aortic bifurcation, thrombosis of one iliac limb occurred, in one immediately and in the other after 18 months. In both instances there was general improvement.

In only one instance of high occlusion was the result tragic. The patient was seen with impending gangrene of the right foot. Vascular symptoms suggesting vasospastic disease developed after a severe injury to the foot. An external iliac arteriogram indicated patency of all vessels. Sympathectomy was not beneficial. An abdominal aortogram demonstrated occlusion of the right common iliac artery. Moderately severe stenosis recurred within 24 hours of endarterectomy. A bypass graft was then inserted. The channel remained open but progressive gangrene of the foot necessitated amputation. The posterior tibial artery was thrombosed.

At the femoropopliteal level, 19 grafts were inserted, with restoration of vascular patency in 15 extremities. In my earliest case, bilateral grafting was performed with homografts pieced out with invalon tubes. Both grafts thrombosed but there has been gradual clinical improvement. In two other cases, grafts ending at the popliteal level failed to function and amputation was necessary. In one of these two cases the runoff was poor. In the other, the cause of failure of two different grafts in the same leg was not apparent.

In all other instances the grafts have remained open and results have been gratifying. Success has been limited in a few cases by uncorrected occlusion at other levels. Some of the most gratifying results have occurred in the six patients with extensive disease requiring treatment at both high and low levels. These six patients had a total of 15 procedures. Two had endarterectomy at the high level and grafts at the low level. In two, grafts extended all the way from the aorta to the popliteal arteries. In the other two, grafts were inserted from the aorta to the femoral artery, and then from the femoral artery another graft extended to the popliteal artery. Circulation was restored in all instances, with four patients having excellent results and two being definitely improved.

This experience suggests that the aphorism, "The longer the graft the more likely the thrombosis," is incorrect and that early experience of that type represented grafts of inadequate length in cases of extensive disease. I am convinced that if one can reach a reasonably good open vessel above and below a properly inserted graft a good result may be expected regardless of the length of the graft.

Stricture of a renal artery was associated with hypertension in three cases. In one 10 year old patient, severe hypertension has been relieved for 18 months after end to side splenorenal arterial anastomosis distal to a stricture in the artery to the left and only kidney. A 32 year old patient had hypertension and a series of strictures in the right renal artery. The hypertension has been relieved for five months after resection of the stenotic segment with end to end anastomosis of the remaining artery. Endarterectomy was ineffective in establishing a lumen in the case of a 60 year old patient with hypertension and severe ste-

FIGURE 4. A 43 year old woman had recurrent right hemiparesis and residual neurologic signs. Stricture of the left internal carotid artery was visualized in the arteriogram. Unbridling of scar tissue completely relieved the symptoms and signs.

nosis of the right renal artery from a sclerotic plaque involving the first centimeter of the vessel, and reanastomosis to the aorta failed. Nephrectomy was performed. Both kidneys were involved with moderately severe nephrosclerosis and the clinical result is equivocal.

Stenosis of the internal carotid artery causing recurrent "partial strokes" and progressive neurologic changes has been relieved in one case by anastomosis of the distal open end of the internal carotid artery to the proximal end of the divided external carotid artery. In a second patient, all symptoms were relieved after the unbridling of a severely stenotic vessel surrounded by a heavy scar apparently caused by previous infection (figure 4).

The only fatality in the entire series was that of a young Negro who was hemiplegic, aphasic and semicomatose on admission six hours after a severe injury which resulted in thrombosis of the proximal portion of the left common carotid artery. This segment was resected and an Edwards-Tapp tube was inserted. The tube remained patent but death resulted from cerebral damage.

Resection and primary anastomosis were successfully performed in two cases of congenital coarctation of the thoracic aorta. One was associated with an aneurysm.

Conclusions

Experience with 43 cases indicates that the reconstructive procedures of thrombo-endarterectomy, embolectomy and grafting usually have been successful in restoring blood flow and relieving symptoms in segmental arteriosclerotic lesions of the abdominal aorta and in the iliac, femoral and popliteal arteries. Complete arteriographic mapping is essential in order to plan adequate comprehensive surgical procedures. For best results an adequate channel must be provided by the reconstruction and the vessels must be open proximal and distal to the graft.

Hypertension resulting from stenosis of a renal artery may be relieved by appropriate correction of the stenosis. Recurrent hemiparetic symptoms due to stenosis of the cervical internal or common carotid artery also may be relieved by definitive repair. The value of a reconstructive procedure in the presence of complete hemiplegia due to cervical arterial occlusion is uncertain.

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Vaginal Bleeding at the Menopause; Investigation and Treatment

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I HAVE practiced gynecology now for nearly 30 years, and the psychologic aspects of menstrual bleeding have been very interesting. Excessive or abnormal bleeding is a source of great consternation to patients, and they complain loudly about it; yet, almost paradoxically, if menstrual bleeding is absent they are panic-stricken, be they 15 or 50.

In addition to describing some of the different forms of vaginal bleeding that we encounter, I want to emphasize the importance of early diagnosis and treatment of cancer by telling you about our work in the diagnosis of early malignancy. We in Montreal have been among the pioneers in cytology; Dr. Ayre worked with me for many years before he moved elsewhere. I will also talk about the endocrine instability of menopausal patients and the damage that may result from giving the wrong form of therapy.

Bleeding is the red flag in gynecology, the danger signal. Regardless of the patient's age, abnormal bleeding indicates that something is wrong. Bleeding from the genital tract can occur at any age from birth to death, and can also denote the most serious of all diseases, cancer. I should like to cite a case treated by Professor Carl Wilson of the University of Rochester. The patient was a twin, and she was 10 months old when vaginal bleeding began. Professor Wilson investigated carefully and found that she had a fast-growing adenocarcinoma of the cervix. He extirpated the uterus and vagina widely, leaving the tubes and ovaries. I have a photograph of the pa-

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tient here, taken when she was 21 months of age, and she appears very healthy; if a careful investigation and prompt treatment had not been carried out, she would not be in this picture.

Abnormal vaginal bleeding is a very common symptom in the age group of 40 to 49 years. Of 10,000 patients who attended the outpatient department of our clinic over a three year period, nearly 45 per cent were in that age group, and they accounted for 34 per cent of all patients who volunteered the information that they had some form of abnormal vaginal bleeding.

Among the multitude of conditions that may cause vaginal bleeding are incomplete abortion, cervical polyp, cervical carcinoma, submucous fibroid, tubal inflammation, tubal pregnancy, ovarian cysts and cystic ovaries. The causes may be grouped into four categories: (1) miscellaneous, (2) new growths, (3) endocrine-menopause and (4) prolonged estrogenic therapy. We are concerned here principally with the last three categories. However, even in patients 40, 45 or 50 years of age, pregnancy must always be considered. Traumatic conditions and inflammatory lesions are not so common. Nevertheless, miscellaneous conditions accounted for some 40 per cent of all cases of bleeding in our clinic among women in the 40 to 49 year age group.

To illustrate the importance of early treatment, I would like to describe a case that had a catastrophic result. It is one of the few such cases in which we have pictorial follow-up material. The patient came to our clinic in 1949 with marked procidentia and erosion of the cervix. Multiple cervical biopsies were done at the time of curettage, and the pathologist reported finding some abnormal cells but no malignancy. The patient refused operation, which would have consisted of wide repair with vaginal hysterectomy. We did not see her again until five years later, and then she had one of the most widespread types of cervical cancer that one will ever see. She died a month later in the hospital. We were unprepared to operate, and she died of complete ureteral obstruction and widespread metastases. Such a patient, we all know, should have been treated to prevent the hazards of malignancy.

Every middle-aged woman should have a periodic checkup, and if there are any questionable or abnormal findings on pelvic examination, probably she should be given the advantage of a cytologic test. Most certainly she should at least have a complete gynecologic examination. All of us can diagnose a definite and clear-cut neoplasm of the cervix such as we see illustrated in textbooks, if we look at it. It has been my experience, however, that physicians often dismiss the patients without a pelvic examination and tell them that their trouble is menopausal bleeding. A year or two later someone else discovers cancer of the cervix. We all can recognize this if we look at it, so it is not any problem if we do our job.

Many years ago, if a patient had a cervical erosion we would have cauterized it and checked it periodically. Today that is not good enough, because in some of these eroded cervices there are small areas of malignant growth. In many cases the Schiller test is still used to show the portion which does not take up the iodine stain—the cells that do not contain glycogen—and biopsies can be taken from the suspicious area. We find that the Schiller test is tedious and hazardous, and can be improved on.

A 27 year old mother of two children came to our clinic because of spotting after coitus. She had moderate prolapse of the uterus and an elongated cervix. We took a cytologic smear and the result of the test was positive. Because of the prolapse and the recurrent spotting, we decided to do a high amputation of the cervix. Had the patient been older, we would not have decided on the conservative approach. Examination of the surgical specimen disclosed carcinoma in situ—one area of cancer in the middle of the slide, a typical picture of the first signs of cancer of the cervix. This case illustrates how valuable a cytologic test may be.

In 1956, we performed 8,499 cytologic tests. In 146 there were abnormal findings, in 27 we found suspicious cells, and in 119 there was definite evidence of cancer of the cervix. Some of you may say that the procedure is

not accurate. I am sure it is not accurate in the hands of someone who lacks a complete knowledge of the procedure, but in the hands of a good cytologist it is accurate, with reservations. In 11 tests the results were negative and the pathologic findings were positive; these are our errors. It is interesting that in these 11 cases only two were cancer of the cervix. We think we can diagnose cervical cancer as well as the pathologist can. When it comes to endometrial cancer we do not make any big boasts—the other nine cases were adenocarcinoma of the endometrium. There were 16 cases in which the results of the cytologic tests were positive and the pathologic reports did not confirm these findings; we will have to wait and see who is right.

Another feature of cytology has to do with the definite atrophic changes that occur in the vaginal and cervical cells in the menopausal and postmenopausal periods. The finding of these atrophic changes would be an indication for estrogenic therapy if the patient had definite menopausal symptoms such as flushes, irritability and bowel disturbances.

Cervical cancer is much easier to distinguish cytologically than endometrial cancer. Normal endometrial cells and the cells of endometrial cancer are very similar; the dark-staining endometrial cells with large nuclei are somewhat misleading to the cytologist.

When we receive a positive cytologic report on a cervical smear, we do not take the report as final. We always corroborate the findings with a pathologic examination. For example, if a positive cytologic test were reported for a multipara who had some patency of the cervical os and slight erosion in the cervical canal, we would follow the cytologic study with the so-called ring biopsy. The first stage is removal of the whole squamocolumnar junction of the cervix. In all, some 18 pielike pieces of tissue are removed, and each is labeled. These pieces of tissue are again sectioned and cut in a paraffin block, and there may be as many as 146 different sections. All are put on slides and examined microscopically by the pathologist. It is a tedious task and an expensive one, and without the support we receive from different societies we could not finance the project. But you can see that we are getting really preclinical cancer, there is no doubt about that.

Now I want to emphasize the great harm that is being done today by improper therapy. Women of every age from 30 to 70 are receiving estrogenic therapy for every type of symptom from falling hair to ingrown toenails. Estrogenic therapy sometimes is improperly prescribed.

The first stage of the normal menstrual cycle is the so-called proliferative phase of the endometrium, coordinating with the ripening graafian follicle in the ovary. With the formation of the corpus luteum following rupture of the ovum, the so-called secretory phase of the endometrium ensues and the glands fill with secretion. Then, if conception does not occur, the corpus luteum regresses and the endometrium undergoes desquamation—the clearing off of the soil, nature being ever expectant of a new pregnancy. A former professor of mine has aptly said that menstruation is the weeping of a disappointed uterus.

As women get older, sometimes this function is incomplete and the ovum does not rupture as it should. With the persistence of the ovarian follicle, the corpus luteum does not form and the endometrium becomes highly hypertrophic. This condition has been labeled Swiss-cheese endometrium, metropathia haemorrhagica, and so on, but it is marked secondary hyperplasia of the endometrium. Estrogenic stimulation is not neutralized with the so-called secretory phase in preparation for desquamation, and so physiologic desquamation does not occur. In a few weeks or months there will be bleeding from necrosis.

Sometimes this condition develops spontaneously; however, frequently it is the result of overloading with estrogenic agents. A physician may prescribe estrogen because the patient is having terrible flushes, and the patient may take the pills for six months or six years, with the result that this hypertrophic, hyperplastic type of endometrium develops and eventually, because of necrosis, will start to bleed. The Novaks as well as many other authors have pointed out that failure of the progesterone reaction to occur after estrogenic

stimulation is a definite predisposing factor to fundal cancer, and we are more and more disposed to agree. In one of our cases, curettage on two occasions showed marked hyperplasia that we diagnosed as metropathia haemorrhagica; four years later a third curettage revealed definite fundal adenocarcinoma.

It is appropriate to warn that when one prescribes estrogenic therapy in moderate dosage there should be at least a lapse of five to seven days each month when the patient does not take estrogen. If a patient who is receiving estrogen therapy begins to have vaginal bleeding and you think it is due to persistent estrogenic stimulation, she is first of all entitled to a curettage. If bleeding recurs a month or two or six months later, perhaps you can give a physiologic curettage, that is, moderate doses of progesterone to mimic the natural phenomenon.

Back in 1944, we opened our well woman's clinic in Montreal. This is perhaps a controversial subject, but nevertheless it is interesting to see what has happened in a 10 year period. In the well woman's clinic we have seen patients early, we have done routine medical examinations and cytologic tests, and I think we see as much preclinical cancer of the cervix as is seen anywhere in America.

In 1946 there were 115 new cases of cancer of the cervix, and in 1956 there were 119. The stages of malignancy of the lesions are quite revealing:

	1946	1956
Stage 1	35 per cent	74 per cent
Stage 2	34 per cent	20 per cent
Stage 3	18 per cent	6 per cent
Stage 4	13 per cent	0

These figures speak for themselves, proving that diligence in examination and early treatment, regardless of the type of treatment, give good results.

In our follow-up clinic we have more than 900 cases of carcinoma of the cervix which we have been following for as long as 25 years. Each year the percentage of living patients is going up, not down. That also speaks for itself. In the absence of a definite clue to the cause of cancer, the next best thing is early diagnosis and early treatment.

Postgraduate Clinical NOTES

95. BLOOD PRESSURE IN ECLAMPSIA

The recording of the blood pressure in the pregnant woman is so important a feature in hospital practice today that it seems hardly credible that as recently as 25 years ago, it was not a routine procedure at all. In 1940 the antenatal case papers supplied to the midwives of a well-known County Council contained no column in which this observation could be noted. This is just one illustration of the state of affairs then pertaining. The blood pressure received attention when the presence of albumin in the urine was noted. The obstetrician, in short, has not been interested in hypertension for very long, which is probably the explanation that we are still not agreed among ourselves as to what we will accept as the upper limit of normal blood pressure, and why we have no common language when we come to discuss the vitally important subject of the hypertensive manifestations in pregnancy.

Keith C. Vartan, Discussion on prevention of eclampsia, *Proceedings of the Royal Society of Medicine*, October 1957, p. 795

Uses and Abuses of Estrogenic Therapy in Gynecology

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In order to assess the value of estrogenic therapy in gynecology one must understand clearly the interrelationships of the various ovarian and pituitary sex hormones. Figures 1 and 2 depict the principal actions and interactions of estrogen, progesterone, and the three hormones from the anterior pituitary gland, follicle-stimulating hormone (FSH), interstitial cell-stimulating hormone (ICSH, also referred to as L. H. or luteinizing hormone), and luteotropic or lactation hormone.

The follicle-stimulating hormone of the anterior pituitary gland stimulates the ovarian follicle to develop and to produce an ovum. The granulosa cells of the follicle produce a rising tide of estrogen which stimulates the endometrium to proliferative activity. The titer of estrogen drops off a little at the time of ovulation, rises again, and then drops markedly shortly before the onset of menstruation. Indeed, the drop in the concentration of estrogen below a certain critical level triggers the onset of menstrual bleeding. Estrogen also inhibits the gonadotropic function of the anterior pituitary gland, thus removing the stimulus for further production of estrogen and resulting in the premenstrual drop.

L. H. or luteinizing hormone stimulates the granulosa cells and the theca cells of the recently ruptured follicle to luteinization. The luteotropic influence on these cells results in production of progesterone, which stimulates the proliferated endometrium to secretory or progestational activity. As in the case of estrogen, because of the drop in gonadotropic activity of the pituitary gland the concentration of progesterone decreases shortly before menstruation. It is, then, this reciprocal action of the ovary and the anterior pituitary gland which is responsible for the periodic character of menstruation.

One should bear in mind that the placenta produces gonadotropinlike hormones (mostly L. H., which is responsible for the results of biologic pregnancy tests) as well as estrogenic and progestogenic substances.

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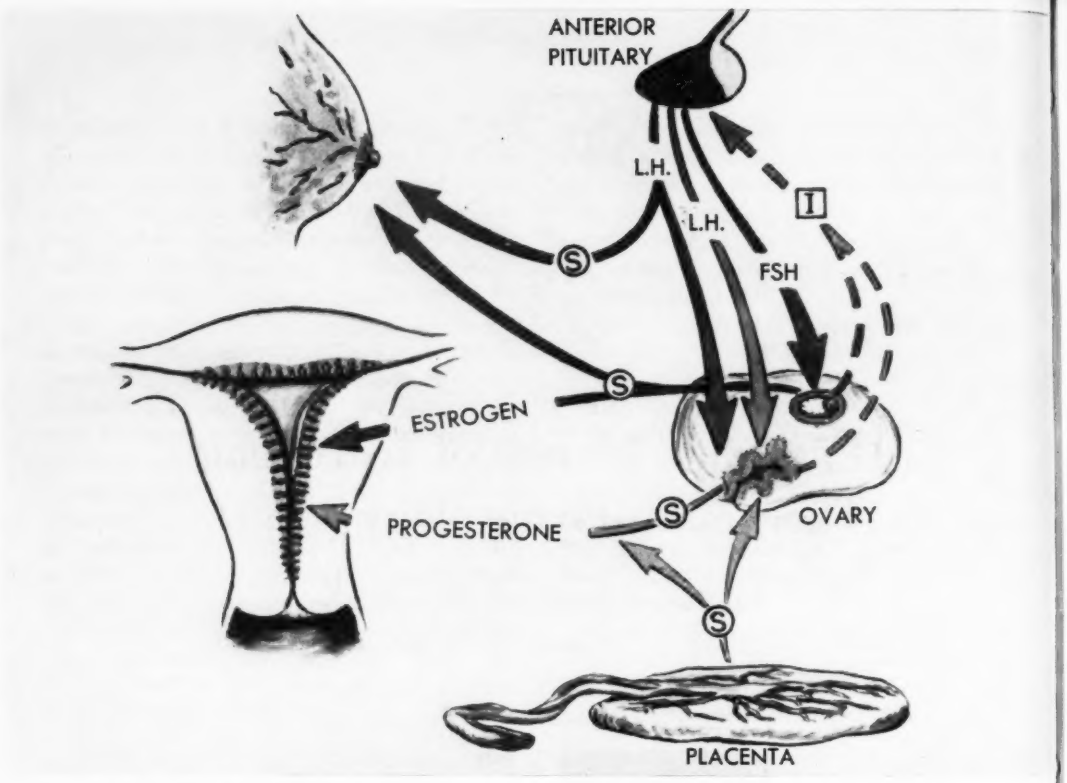
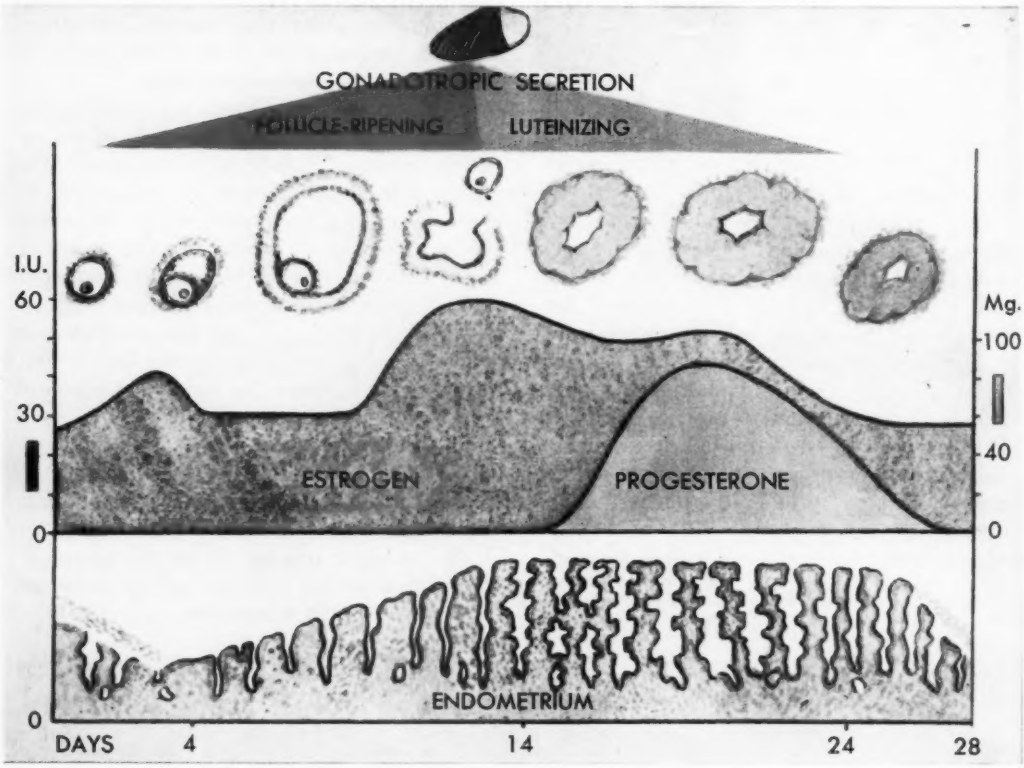


FIGURES 1 and 2. Actions and interactions of estrogen, progesterone, follicle-stimulating hormone, interstitial cell-stimulating hormone, and luteotropic hormone.



When the ovaries are absent or refractory to the action of gonadotropic hormones because of disease or aging, too little estrogen is manufactured to suppress the gonadotropic function of the anterior hypophysis, which proceeds to produce excessive quantities of FSH. Some observers believe that this phenomenon is responsible for menopausal symptoms. In any event it is clear that the whole process depends basically on the lowered titer of estrogen.

If estrogenic action is not supplemented by that of progesterone, overgrowth of the endometrium may result, frequently accompanied by hypermenorrhea.

Estrogen stimulates the duct system of the breasts and is responsible for the engorgement which so often precedes menstruation. It also accounts for development of secondary sex characters (breasts, external genitalia, female escutcheon, and possibly the shape of the bony pelvis). In addition, estrogen stimulates early closure of epiphyses and favors calcification of bone.

The gonadotropic hormones do what their names imply. Actually the commercial products available, while definitely active in animals, do not have well-marked actions in humans. Since they are protein substances, their injection may lead to antihormone formation.

Clinical Uses of Estrogen

The principal conditions for which estrogenic therapy has been used are as follows:

1. Menopausal symptoms.
2. Hypermenorrhea (menorrhagia).
3. Amenorrhea.
4. Osteoporosis.
5. Endometriosis.
6. Senile vaginitis.
7. Advanced cancer of the breast in postmenopausal women.
8. Infertility.
9. Suppression of lactation.
10. Dysmenorrhea.
11. Diabetes in pregnancy.
12. Abruptio placentae.
13. Threatened and habitual abortion.

I believe that estrogenic therapy is distinctly valuable in many of these situations and that oral preparations usually are the most appropriate and useful. Many workers have cautioned against long-continued use of estrogen in fear of creating conditions favorable to cancer. It is well known that large doses of estrogen lead to a greatly increased incidence of breast cancer in certain strains of mice. Cancer of the cervix also has been produced in these animals when they have been protected from the death which otherwise comes much sooner from cancer of the breast.

While we should exercise some caution in allowing women to take estrogens over long periods in an unsupervised manner, the danger of inciting conditions favorable to formation of cancer probably is slight. The amount of estrogen per kilogram of body weight is infinitesimal compared with the doses used in mice. In fact, I know of no authenticated instance in which cancer has resulted from administration of estrogen to human beings, even though some women have received large doses over long periods. A few cases of carcinoma of the endometrium have been reported in association with use of estrogens but a causal relationship was not clear. Even larger doses administered to monkeys have also failed to produce cancer.

A second principal reason advanced for curbing the use of estrogens is the uterine bleeding which excessive doses often produce. While it is important to recognize this possibility, one can almost always overcome the bleeding problem by lowering the dosage or by stopping the estrogen if bleeding continues in spite of adjustment of dosage.

Menopausal symptoms—Hot flushes, nervousness and insomnia disturb menopausal women in varying degree and rarely appear before menstruation has become quite irregular or has ceased. At least one-third of all women experience little or no discomfort at this time. Perhaps 10 per cent have severe symptoms—or react strenuously to their symptoms. The remainder, or well over half of all women, have moderate discomfort. Physiologically, the estrogen titer decreases and the concentration of FSH increases at the menopause. Many authorities attribute menopausal symptoms to the increased concentration of FSH

rather than to the decrease in estrogen.

In my opinion, estrogens have a distinct place in treatment of menopausal symptoms. They are effective in relieving all but a few. Whether they act intrinsically or by suppressing the gonadotropic function of the anterior hypophysis is not known for certain. One should try to find the smallest dose which will produce the desired effect, and can start with a tiny dose and work up or start with a sizable dose and work down. For example, one might prescribe diethylstilbestrol in a dosage of 0.1 mg. daily for one week and increase the dosage by 0.1 mg. each week until the minimal effective dose is reached. The effective dose should then be continued in a cyclic or an interrupted fashion—for example, every day for three weeks, and then discontinued for a week as in nature. Or one can prescribe estrogen for six days of the week and then omit therapy one day. Taken in this manner, estrogen remains effective yet there is little danger of inciting bleeding.

Natural estrogens such as ESTINYL® and PREMARIN® are equally satisfactory but much more expensive than diethylstilbestrol. The nausea that sometimes accompanies administration of stilbestrol is related to the dose, I believe, and not to any characteristic of the drug. Generally, stilbestrol given orally in a dosage of 0.5 mg. per day for six of the seven days in a week will relieve menopausal symptoms. According to my experience, estrogens administered by any other route for menopausal symptoms are practically never indicated.

Patients receiving estrogens regularly should be examined regularly. In due time, usually in less than a year, the physician can encourage reduction in dosage. Most women do this spontaneously as time passes and as they become adjusted. They forget to take the medicine and do so only when symptoms return in times of stress, until finally there is no further need and they stop taking the hormone.

Hypermenorrhea (menorrhagia)—Estrogenic therapy frequently is useful to control excessive or too frequent menstruation not due to uterine fibromyomas or malignancy. It appears that there is a critical level of estrogen below which uterine bleeding occurs and above which it does not. When excessive menstrual bleeding occurs, raising the level of estrogen by administering such substances orally, intramuscularly or possibly intravenously often results in cessation of bleeding.

Before employing estrogenic therapy for hypermenorrhea one must rule out the presence of definite local pathologic conditions such as endometrial polyp, fibromyoma, other uterine tumors and ovarian neoplasms. Generally a curettage is done before estrogenic therapy is started, although occasionally it seems reasonable to give estrogen on a trial basis without curettage. However, curettage should not be delayed too long if bleeding persists. This type of hypermenorrhea is characteristic of the adolescent and premenopausal years and is often associated with failure of ovulation. Hormonal therapy—in fact, any conservative treatment—is especially applicable when the patient is young. It is less applicable and less satisfactory for patients in their middle and late forties. Then, something more definite is usually demanded, and necessary. While hormonal therapy is substitutive only, it sometimes assists in tiding the young patient over several bad years.

Usually I administer estrogens orally for hypermenorrhea. In a given bleeding episode I might start the patient on a daily dose of 0.5 mg. stilbestrol for two days and increase the dose by 0.5 mg. daily until she is taking 2 to 3 mg. or until bleeding ceases. I might then reduce the dose to 1 mg. a day and continue this for three weeks, expecting bleeding not to occur again for several days after withdrawal of the hormone. When bleeding starts I would repeat the course of estrogenic therapy. This, of course, is an effort to imitate the natural cyclic rise and fall of this hormone, and it often works well for limited periods. The advice of Hamblen, Holmstrom and others to give progesterone also in such cases, especially if failure of ovulation has been demonstrated, is quite popular. The progesterone would be added at mid-cycle and continued for 12 days, thus imitating nature even more closely. While such a regimen is entirely logical, it has not been clearly shown that administration of progesterone adds much to the

control of bleeding. According to Karnaky, one often can stop bleeding of the type under discussion quite abruptly by injecting a sizable dose of estradiol or other potent estrogen into the anterior lip of the cervix.

Amenorrhea—Amenorrhea and hypomenorrhea often are due to causes other than mere insufficiency in ovarian production of estrogen. The first requisite in treating such conditions is diagnosis of the cause. If it cannot be corrected at its source and the patient has a uterus, one can produce cyclic bleeding from a proliferative endometrium by administering estrogen in cyclic fashion as already described. One can imitate nature more closely by adding progesterone in the second half of the cycle. It should be appreciated that this is substitution therapy only and that the condition will return when hormones are withdrawn.

There are occasional cases in which incomplete uterine development is accompanied by amenorrhea, and administration of estrogen and progesterone may cause growth of the uterus with subsequent improvement in the menstrual pattern even after the hormones are stopped. Sometimes, cyclic bleeding is of great psychologic value for the amenorrheic girl. Administration of estrogen and progesterone is indicated in a restricted number of instances of amenorrhea or hypomenorrhea, but only after a careful diagnosis has been made.

Osteoporosis—Estrogens definitely have a beneficial effect in osteoporosis. Their exhibition results in improved calcification. Unless there are specific contraindications to their use, one should prescribe moderate daily doses. Doses should be kept below the level at which bleeding occurs, and the hormone should be given in an interrupted manner as described for menopausal symptoms.

Endometriosis—The proliferative effects of estrogen on endometrium would seem to contraindicate estrogenic therapy in endometriosis. Karnaky has reported that *large* doses of estrogen, sufficient to suppress the gonadotropic function of the anterior pituitary gland and consequently menstruation, are beneficial in this condition. A number of other workers have confirmed this observation. Scott did not find this true, however, in experimental endometriosis in the monkey. The plan is to start with small doses and increase them rapidly and as necessary, even to several hundred milligrams of stilbestrol daily—the important thing being to give enough to suppress bleeding. Actually, beneficial results have been observed when periods of amenorrhea have been produced by other means such as a pregnancy or radiation of the ovaries. However, since the diagnosis of endometriosis is necessarily a clinical one based on palpatory findings in the pelvis in almost all instances, long-term results are difficult to assess. Use of estrogenic therapy for endometriosis must remain *sub judice*.

Senile vaginitis—The atrophy of vaginal mucosa that comes in the postmenopausal years often is associated with an irritating discharge and sometimes with infection as well. As might be expected, administration of estrogens either by mouth or locally in vaginal ointment form stimulates growth of the squamous epithelium and thereby alleviates the discomfort in large measure. One must take care to keep the dosage below the bleeding level.

Advanced cancer of the breast (with metastases) in postmenopausal women—Estrogenic therapy has been used in advanced cancer of the breast, especially when metastases have been present, particularly bony metastases. There has been evidence of alleviation of symptoms and even of disappearance of lesions. The good results have been obtained mostly in postmenopausal women. Quite large doses have been used. The rationale for this therapy is not clear except in regard to the bone destruction due to osseous metastases. Possibly suppression of the pituitary gland is the explanation. Certainly any agent that will alleviate symptoms under the conditions specified is worth using. Paradoxically, in all other circumstances connected with breast cancer every effort is made to be rid of the influence of estrogen, even to the point of castration and adrenalectomy.

Infertility—In some cases of infertility the uterus is subnormal in size and the endometrium is scanty and relatively unresponsive. Often there is an associated hypomenorrhea or amenorrhea. Estrogenic therapy may be of some value in stimulating growth and devel-

opment. My experience in this regard has not been too encouraging. However, if other explanations for the infertility have been ruled out, a trial of estrogenic therapy is not contraindicated. Dosage should be roughly equivalent to 5 mg. of stilbestrol daily.

Suppression of lactation—If a patient does not wish to nurse her baby or if breast feeding is unwise, engorgement and lactation can be suppressed by the early exhibition of estrogen or androgen, or both. Presumably the hormones suppress the ability of the anterior pituitary gland to produce the lactation hormone. Administration of hormones must be started the day of delivery and continued in gradually diminishing doses for six weeks.

It has been alleged that estrogen causes uterine bleeding when it is finally withdrawn. This has not been my experience in administering this hormone in the puerperium. For this reason and because estrogen is cheaper and easier to administer, I prefer it to androgen. I do not object to combinations but I see no special virtue in them. Estrogenic therapy is successful in suppressing lactation in approximately 90 per cent of the cases when it is given in the manner described. We have not found it possible to stop lactation by using hormones once it has become established. A suggested regimen is as follows: stilbestrol (or equivalent), 5 mg. daily for 10 days, 4 mg. for four days, 3 mg. for three days, 2 mg. for two days, and 1 mg. daily until the six week period is complete. Recently, success has been reported with a single intramuscular dose of a long-acting depot type of estrogen.

Dysmenorrhea—Menstruation following ovulation is often accompanied by cramps. Anovular bleeding rarely is associated with purely physical discomfort. Estrogen given in the early postmenstrual days can suppress ovulation and thus can produce painless menstruation. This is not a permanent solution to the problem of dysmenorrhea, and therefore the use of estrogens is indicated in this condition only as a temporary measure or to gain the confidence of the patient.

Diabetes in pregnancy; abruptio placentae; threatened abortion; habitual abortion—According to Olive and George Smith, all these conditions often are associated in some way with failure of the placenta to produce an adequate supply of progesterone. They believe that administration of stilbestrol in increasing doses provides a missing link which results in the correction of the deficient hormonal status. The evidence for such a belief is by no means clear.

In diabetes in pregnancy, Priscilla White supports the Smiths' contention and believes that administration of stilbestrol during the pregnancy has improved the prognosis for the fetus over that which good medical management alone can achieve. Her figures are as good as or better than those reported from other sources, in the neighborhood of 90 per cent fetal survival. Eastman, Reis and others with large experience in this field doubt the value of the stilbestrol. This much can be said: No one has reported bad effects from giving the stilbestrol. If one does use stilbestrol for diabetes in pregnancy one should do so with full realization of its doubtful value.

Use of estrogenic substances in threatened or habitual abortion and abruptio placentae is of even more doubtful value and is not advised at this time. Indeed, in cases of threatened abortion their use has often seemed to lead to missed abortion.

Recently, combinations of estrogens and androgens have been widely advised and advertised. Their supposed value lies in the neutralization of the feminizing and masculinizing effects of the estrogen and the androgen, respectively, yet reportedly they retain their ability to suppress gonadotropic function. These are good theoretical advantages. However, I believe that the superiority of such preparations over estrogen alone has not been established.

Abuses of Estrogenic Therapy

The principal abuses in estrogen administration are as follows:

1. Administration of estrogenic substances for vague and poorly understood symptoms before the menopause has really started. Estrogen often is given in desperation when an explanation cannot be found for the symptoms of a patient nearing the menopausal age. Ex-

h bition of estrogen in this manner not infrequently masks the true state of affairs and often leads to abnormal bleeding.

2. Continuous administration of estrogen after menstruation has ceased. When given without interruption, estrogen often produces abnormal bleeding and sometimes is responsible for development of cystic masses in the breasts.

3. Continuation of medication over a period of many years *may* be dangerous in that it may lead to endometrial hyperplasia—and eventually to adenocarcinoma of the endometrium, although such a sequence has not been proved definitely. Most authorities recognize some relationship between estrogen metabolism and endometrial carcinoma, and some experts feel that the stimulating effect of estrogen on the duct epithelium of the breasts may lead to breast cancer. We know that the incidence of endometrial carcinoma is significantly higher among persons with certain theca and granulosa cell tumors of the ovary (estrogen-producing tumors) than it is under ordinary circumstances.

4. Administration of estrogens intramuscularly on a regular schedule without proper checkups is to be deplored, yet estrogen is employed widely in this manner. To put it mildly, this method of treatment is both unnecessarily complicated and expensive for the patient.

5. While there is no definite proof that estrogen is dangerous in the doses employed in patients who have been treated for cancer of the breast and of the endometrium, it is probably safest not to use it in such cases.

Estrogen is by all odds the most useful of the hormones employed in gynecology today. When proper precautions are observed there is little chance that estrogenic therapy will lead to development of cancer in the genitalia or breasts. Estrogens especially, but to some extent other hormones also, have frequently been used unwisely. The chief abuses have been (1) use without a proper diagnosis, (2) uninterrupted dosage, and (3) intramuscular injection when oral medication would suffice or even when oral therapy would surpass intramuscular administration.

Postgraduate Clinical NOTES

96. USE OF THYROID HORMONE IN GYNECOLOGY

Infertility, menstrual irregularities, amenorrhea, hypermenorrhea and, possibly, abortion have all been associated with hypothyroid states. Sometimes these conditions have seemed to respond to thyroid therapy even when no definite hypothyroidism could be demonstrated. For these reasons it is justified, I believe, to use thyroid empirically when such conditions exist and other more specific forms of treatment have failed. Thyroid therapy should always be administered under supervision, however. Probably the effect of the drug has not been really tested unless the dose has been gradually increased to tolerance; one should drop back from this level for continued administration.

Daniel G. Morton, Uses and abuses of hormone therapy in gynecology, *Chicago Medical Society Bulletin*, July 27, 1957, pp. 61-68

Indications for the Use of Oral and Parenteral Diuretics

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THERE have been three epochal advances in the treatment of congestive heart-failure: (1) the application of digitalis in 1785, (2) the introduction of salt restriction in 1904, and (3) the introduction of mercurial diuretics in 1919. The beneficial effect of each of these measures is due largely or entirely to diuresis. However, of the two medicinal agents, only the mercurial drugs are diuretics in the strict and specific sense that they function solely by increasing the volume of urine by their primary action on the kidneys. On the contrary, diuresis produced by digitalis is due predominantly, if not solely, to improved function of the heart.

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Organic Mercurial Diuretics

In congestive heart-failure, which is the most common indication for a diuretic, the organic mercurial diuretics are almost always the most effective drugs for supplementing digitalis. If diuresis can be produced by any medicinal agent, that resulting from the use of a mercurial diuretic will be the most copious. It is difficult for the young physician to realize how completely the clinical picture of congestive heart-failure has changed since these diuretics began to be used generally. In the wards of hospitals, physicians no longer see cases of cardiac disease in which the patients are unrecognizable because of swelling of the face and closure of the eyelids, patients who have fluid draining from rupture of the skin of legs which are enormously distended as a result of edema, and cases in which the prepuce must be incised in order to permit micturition.

The mercurial diuretics have greatly pro-

onged the average duration of life after the heart has failed, and they often enable the patient to pursue an occupation for years longer than would be possible if treatment were limited to the restriction of salt and the administration of digitalis. Along with the advancing age of the population and the conquest of infectious diseases, mercurial diuretics account for the higher proportion of cardiac patients in the medical wards.

Like all potent drugs, mercurial diuretics have their disadvantages and dangers. NOVASUROL®, the first mercurial diuretic to be introduced, was indeed quite toxic. When mercurial diuretics were first introduced, they often were administered intravenously, which on rare occasions led to sudden death. However, the mercurial diuretics that are being used at present have an extremely low degree of toxicity, and they very rarely are administered intravenously. Immediate fatal reactions do not occur after the intramuscular or subcutaneous injection of these drugs. If they are not given to patients with azotemia due to intrinsic renal disease, mercurialism resulting from the cumulative action of repeated doses rarely occurs. Although fever, rashes and other manifestations of hypersensitivity occasionally necessitate discontinuance of administration of these drugs, these reactions are not dangerous. The fact that millions of injections of these diuretics have been given in recent years is evidence that they are among the safest of potent drugs used in the treatment of serious illness.

Parenteral and Oral Administration of Mercurial Diuretics

Until recently, mercurial diuretics were administered almost solely by the intramuscular route. However, in a large majority of cases, MERCUHYDRIN® and a solution of THIOMERIN® sodium can be injected subcutaneously without causing too much irritation. When these diuretics are administered in this manner, diuresis occurs a little more slowly than it does when they are administered intramuscularly, and the increase in the excretion of urine seems to be only slightly, if any, less than it is when the diuretics are injected intramuscularly. In an appreciable number of cases, self-administration of the diuretic is necessary. In these cases, the subcutaneous method of administration is the one of choice if it does not produce much local irritation, which it usually fails to do. It is important to note that, in cases in which Mercuhydrin or a solution of a similar mercurial diuretic is being administered, increasing the dose above 2 cc. rarely if ever will augment the diuresis, and, of course, will favor the occurrence of undesirable side effects. For this reason, if a dose of 2 cc. does not produce satisfactory diuresis, the dose should not be increased. However, a dose of 2 cc. of Mercuhydrin often produces better diuresis than a dose of 1 cc.

Effective mercurial diuretics now are available for oral administration. My experience with these diuretics has been limited to NEOHYDRIN®, which is effective in many cases of mild or even moderately severe congestive heart-failure. In cases of severe congestive heart-failure, parenteral administration of a mercurial diuretic is necessary, at least when treatment is begun, and usually as a periodic supplement to the oral administration of the diuretics. In all cases of congestive heart-failure except those in which the disease is very severe, the frequency of injections of mercurial diuretics and the associated side effects can be lessened by administering the diuretic orally. In cases in which the diuretic is administered only by the oral route, the patients often get along well. The value of administration of the diuretic in this manner is evidenced by a prompt gain in weight when use of the diuretic is discontinued.

Although increasing the parenteral dose of Mercuhydrin to more than 2 cc. does not increase diuresis, increasing the oral dose of Neohydrin does augment diuresis. This is presumably due to the absorption of only a fraction of the dose, perhaps 15 per cent, and doubtless even less in the presence of congestion and edema of the alimentary tract.

Unfortunately, a metallic taste, anorexia, abdominal discomfort or cramps, nausea, vomiting or diarrhea develops in an appreciable number of cases in which mercurial diuretics are administered orally, but these symptoms

rarely necessitate discontinuance of administration of the diuretics. Gingivitis and stomatitis usually can be averted by good oral hygiene. They perhaps are due to liberation of ionic mercury from the diuretic.

The administration of mercurial diuretics can be continued for years, and even for a decade or more, without the development of a cumulative action. In many cases, hundreds of injections have been administered without causing any ill effects. It was formerly thought that long-continued administration might injure the kidneys, but this does not appear to be true. The regressive tubular lesions which have been attributed to the toxic action of mercurial diuretics have been found just as often in cases of severe congestive heart-failure in which these diuretics have not been administered as they have been in cases in which these diuretics have been used. These lesions evidently are due to circulatory failure.

Indications for the Use of Mercurial Diuretics

Congestive heart-failure is the outstanding indication for the use of an organic mercurial diuretic. This is true even if there is no pitting peripheral edema, and even if physical or roentgenographic examination does not reveal any evidence of pulmonary edema. The scale shows that as much as 10 or 15 lb. of fluid can be retained without producing these signs. It is true that congestive heart-failure can be relieved by salt restriction and the administration of digitalis in a high percentage of cases. However, the improvement almost always can be accelerated by the use of a mercurial diuretic, and it often cannot be attained at all without the use of this diuretic. Since a vicious cycle exists in the sense that congestion resulting from heart-failure tends to augment the cardiac insufficiency, it seems rational to hasten the improvement by administering a mercurial diuretic, especially since it is safe if properly used. Mercurial diuretics are indicated in all the etiologic types of heart-failure, whether they involve the right or left side of the heart, and whether they are associated with a high or low cardiac output.

In cases of nephrotic edema, whether due to glomerulonephritis, chronic (lipoid) nephrosis, disseminated lupus erythematosus or amyloidosis, a mercurial diuretic may produce copious diuresis. This is especially likely to occur if hyperchloremic acidosis has been produced by the daily administration of 6 gm. of ammonium chloride for two or three days. Unfortunately, even more often, mercurial diuretics fail to relieve the edema of hypoproteinemia, and, when they are initially effective, their efficacy usually diminishes. Only exceptionally will mercurial diuretics keep hypoproteinemic patients free of edema for many months when the use of sodium restriction alone does not suffice.

A mercurial diuretic may produce diuresis in a case in which ascites is due to cirrhosis of the liver, but the diuresis rarely is sufficient to influence the clinical course of the disease significantly.

The fluid retention which plays an important part in producing the symptoms of premenstrual tension usually is prevented or relieved by a mercurial diuretic. However, this often can be accomplished by means of mild salt restriction supplemented by the use of a nonmercurial diuretic such as DIAMOX®, ROLICTON® or DIURIL®.

Mercurial diuretics often have been included in the regimen for the reduction of weight in cases of obesity. It has not been demonstrated, however, that they improve the results obtained with caloric restriction, and their use is hardly justified in cases of uncomplicated obesity.

Contraindications to the Use of Mercurial Diuretics

The mercurial diuretics are among the safest of potent drugs, and there are few contraindications to their use. They are ineffective and should not be administered in acute glomerulonephritis associated with hematuria and in cases of necrosis of the renal tubules (lower nephron nephrosis). In the former condition, they may augment the hematuria; in cases of the latter condition, it has seemed to me that these mercurial diuretics have aggravated the oliguria.

These diuretics should not be used in cases

with significant azotemia (cases in which the value for the nonprotein nitrogen is more than 60 mg. per 100 cc. of blood) due to intrinsic renal disease. In such cases, these diuretics rarely increase the volume of urine and even may decrease it, and their administration may be followed by erythrocyturia. On the other hand, with moderately severe azotemia and even with severe proteinuria as the result of congestive heart-failure, mercurial diuretics may be very effective and may decrease the severity of both azotemia and proteinuria.

Mercurial diuretics should be used with caution in cases of prostatism, especially if the patients are bedridden, because sudden distention of the bladder may lead to complete urinary retention. In cases of severe cerebral arteriosclerosis, copious mercurial diuresis may precipitate disorientation, hallucination, somnolence and other severe cerebral symptoms. In a few cases, it has seemed to me that cerebral thrombosis was brought on by a concentration of the blood following a mercurial injection.

The most frequent contraindication to the use of these diuretics, however, is their failure to produce satisfactory diuresis. If a subcutaneous injection of 2 cc. of Mercuhydrin or a solution of a similar preparation does not produce diuresis, or fails to do so despite previous preparation of the patient by the administration of ammonium chloride or after subsequent potentialization by intravenous administration of aminophylline, no good purpose is served by continuing the administration of a mercurial diuretic unless there is some improvement in the underlying condition of the patient. No benefit is gained by increasing the dose to more than 2 cc. or by changing the type of mercurial diuretic that is being administered. It recently has been observed that slow intravenous administration of the diuretic by the drip method is effective in cases in which the subcutaneous administration is ineffective, but I have not had any experience with this method.

Patients with active peptic ulcer, ulcerative colitis or irritable colon usually cannot tolerate mercurial diuretics when these preparations are administered orally.

Loss of Response to Mercurial Diuretics

In many cases, congestive heart-failure can be averted or controlled for many years by salt restriction and by the administration of digitalis and mercurial diuretics. Unfortunately, sooner or later, unless an intercurrent disease proves fatal, the mercurial diuretics cease to be effective. This usually is an ominous prognostic sign which heralds the beginning of the final stage of the cardiac disease. Although refractoriness to these diuretics may appear suddenly, it usually develops gradually as more frequent injections are required to avert the restriction of fluids. Why a patient who has responded satisfactorily to the administration of mercurial diuretics no longer does so often is not clear. This is not due to the development of tolerance in the sense that the term is applied to hypnotics and narcotics, for increasing the dose does not produce diuresis.

Refractoriness appears to be due to multiple causes. These drugs produce diuresis by inhibition of enzymes which participate in the tubular reabsorption of chloride* ions from the glomerular filtrate. The increase in urinary volume is due to osmosis of water caused by the chloride and sodium ions which are not reabsorbed and finally are eliminated in the urine. It appears probable, although this perhaps is an oversimplification, that the causes of the refractoriness are factors which diminish the amount of chloride delivered to the renal tubules by the glomerular filtrate. Under these circumstances, the amount of chloride reaching the tubular cells is within their reabsorptive capacity, although this has been greatly decreased by the action of the mercurial diuretic. Such a decrease in the amount of chloride in the tubular fluid may be due either to a decrease in the volume of fluid filtered by the glomeruli or to hypochloremia associated with a low concentration of chloride in the glomerular filtrate.

By far the most common cause of refrac-

*There is considerable evidence, although not conclusive, that the action of mercurial diuretics is primarily on reabsorption of chloride and that the sodium diuresis is a secondary phenomenon.

toriness is intensification of heart-failure. This brings in its wake diminished cardiac output (apart from cases of high-output failure), renal arteriolar constriction, decrease in renal blood flow and glomerular filtration, and consequently a diminution in the amount of chloride filtered to less than the reabsorptive capacity of even the mercurialized tubular cells. With the decrease in cardiac output, the secretion of salt-retaining adrenal corticoids is augmented.

Less frequently, the refractoriness is the result of diminution in the concentration of chloride in the glomerular filtrate due to hypochloremia. Exceptionally, the hypochloremia (and the hyponatremia) is due to a combination of such factors as protracted restriction of salt, anorexia, excessive use of mercurial diuretics, and vomiting caused by digitalis intoxication and hepatic and gastrointestinal congestion.

More often, however, in cases of congestive heart-failure, hyponatremia and hypochloremia are due, at least partially, to dilution. In such cases, rigid restriction of sodium chloride in the diet is not accompanied by a corresponding restriction in the intake of water. As a result, more water is ingested than the kidneys can excrete, and dilution of extracellular fluid occurs. Often, indeed, intravenous infusion of a sugar solution, given in the hope that it will combat azotemia, aggravates the hypotonicity of the extracellular fluid. In many cases of far-advanced congestive heart-failure, the cause of hyponatremia and hypochloremia is entirely obscure. Apparently, the sodium and chloride ions are transferred from the extracellular fluid to the cells, and the concentration of sodium and chloride in the plasma cannot be increased by infusions of saline solution which the patients can tolerate.

If refractoriness to mercurial diuretics occurs in a case of congestive heart-failure, the following measures should be tried in an effort to restore the responsiveness. If digitalis has not been administered in optimal doses, such doses should be administered. The concentration of chloride in the plasma should be increased by the daily administration of 6 to 9 gm. of ammonium chloride in the form of enteric-coated tablets for two days before the mercurial diuretic is to be injected and on the day following the injection. If the patient is vomiting and cannot tolerate the oral administration of ammonium chloride, the drug may be administered intravenously in the form of a 1 per cent solution in a 5 per cent solution of dextrose. Not more than 1000 cc. of the solution (10 gm. of ammonium chloride) should be infused slowly in one day, and this should be given in divided doses. Ammonium chloride should not be used in cases in which intrinsic renal disease is associated with azotemia, nor in cases in which hepatic function is impaired. It may cause severe or even fatal acidosis in the former group of cases, and it may cause ammonium poisoning in the latter.

If supplementing the mercurial diuretic with ammonium chloride does not produce satisfactory diuresis, subsequent administration of aminophylline occasionally may be effective.[1,2] One-half gram of this drug should be injected intravenously one or two hours after the administration of the mercurial diuretic. The aminophylline presumably increases the renal blood flow and thus augments the amount of chloride reaching the renal tubules.

If congestive heart-failure associated with hyponatremia fails to respond to the administration of a mercurial diuretic, the possible presence of "dilution hyponatremia" should be suspected. This may result from the ingestion of more water than can be excreted or from intravenous infusions of solutions of dextrose. If the history indicates that the hyponatremia is due to either of these causes, the daily intake of fluid should be restricted to a liter for several days. This restriction occasionally results in an increase in the concentration of sodium and chloride in the serum and a return of responsiveness to the mercurial diuretic.

In some cases of congestive heart-failure in which refractoriness to the mercurial diuretics occurred, Rubin and his associates[3,4] were able to restore responsiveness by producing hyperchloremic acidosis by administering both Diamox and ammonium chloride. After diuresis had been established, it was found that the increase in the aqueous component of the urine was proportionately greater than the

ncrease in the sodium. As a result, the hypo-atremia was corrected.

Unfortunately, however, congestive heart-failure ultimately reaches a stage at which none of these measures will restore the efficacy of the mercurial diuretics. This probably is most often due to a decrease in glomerular filtration to so low a level that even the mercurialized tubule reabsorbs almost all of the filtered chloride.

Nonmercurial Diuretics

The older nonmercurial diuretics, of which the xanthines were the most widely used, were actually of little value, and their use has been generally abandoned. Recently, however, new types of nonmercurial diuretics have been synthesized as a result of planned research. Of these, the carbonic anhydrase inhibitor Diamox (acetazolamide) is the most widely used.

By inhibiting the formation of carbonic acid in the cells in the distal portion of the renal tubules, Diamox lessens the exchange of hydrogen ions for sodium and other basic ions in the tubular fluid and thus favors diuresis. The optimal diuretic effect is obtained by administering a dose of not more than 250 mg. once a day. Nothing is to be gained by administering larger doses.

Diamox often produces considerable diuresis in cases of mild or moderately severe congestive heart-failure and in cases of premenstrual tension. It is of little value in treating either severe congestive heart-failure or the nephrotic syndrome. Unfortunately, the diuresis produced by this drug decreases rapidly if administration of the drug is continued for more than two days. This decrease in efficacy is perhaps due to compensation for the acidosis produced by the drug and to a decrease in the enhanced secretion of bicarbonate. Diamox, therefore, should be administered in courses, and 250 mg. should be administered daily for not more than two or three days.

Ford, Spurr and Moyer[5] found that the natruresis produced by Diamox is about equal to that produced by the daily administration of three Neohydrin tablets for two days. They likewise found that the natruresis and diuresis produced by Neohydrin did not decrease when the administration was continued. On the other hand, there was a decreasing response to the continued administration of Diamox.

The combined use of Diamox and ammonium chloride to produce hyperchloremia and thereby combat refractoriness to a mercurial diuretic already has been mentioned.

Diamox sometimes is useful in the treatment of cor pulmonale. In addition to its usual diuretic effect, it lowers the increased concentration of serum bicarbonate and also lowers the carbon dioxide tension. However, since Diamox produces metabolic acidosis, care should be taken in administering it if respiratory acidosis is extreme.

Rolicton, an aminouracil, has been introduced recently as an oral diuretic. It perhaps acts by inhibiting tubular reabsorption of sodium. It often is an effective diuretic in cases of mild congestive heart-failure. Four tablets, each containing 400 mg., are administered on the first day. Thereafter, diuresis is maintained by the daily administration of two tablets. I have found that this diuretic is of little value in the treatment of severe congestive heart-failure or the nephrotic syndrome.

In my experience, it has been exceptional when either Diamox or Rolicton has been as effective as Neohydrin in cases of congestive heart-failure in which the patients have been able to take adequate doses of this drug.

Space permits little more than brief mention of the cation exchange resins. When administered daily in doses of 45 to 60 gm., they may produce diuresis in cases of congestive heart-failure or the nephrotic syndrome, and thus improve renal function. In some cases of nephrotic edema, they produce spectacular diuresis after other measures have been ineffective. However, few patients will take the disagreeable bulky powders for long periods, and their use has decreased in recent years.

I shall not discuss the use of corticosteroids and ACTH in the treatment of the nephrotic syndrome, although they are by far the most effective diuretics in most cases of uncomplicated nephrotic syndrome, especially in cases in which the patients are children. They have revolutionized the treatment of this syndrome, and have improved the prognosis.

It may be mentioned, moreover, that, seemingly paradoxically, corticosteroids and ACTH sometimes produce diuresis in cases of congestive heart-failure.[6, 7] In some cases of refractory congestive heart-failure, the daily administration of 20 to 40 mg. of prednisone may produce diuresis or restore responsiveness to the mercurial diuretics. These effects may occur immediately or only after the prednisone has been administered for several days. In most cases, however, prednisone is ineffective. The mechanism of the diuretic action remains to be elucidated, but inhibition of secretion of aldosterone or competition with it in the renal tubular cell may be concerned.

ADDENDUM

Since this paper was written, I have had the opportunity to use chlorothiazide (Diuril), a newly synthesized natruretic and diuretic. It appears to be a valuable oral diuretic, which in many instances of congestive failure can replace mercurial injections.

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Postgraduate Clinical NOTES

97. THE GENERAL PHYSICIAN AND RADIATION

The general physician utilizing x-ray equipment or isotopes must provide radiation protection for his personnel in the same way as the radiologist, or possibly 10 times more so. In other words, a person in the field of radiation working in an area of occupancy is allowed to receive 10 times more radiation than one who is not (the man in the street or the physician's secretary). An area of occupancy is under the control of a radiation safety officer. The total dosage to personnel, as well as interval blood counts, should be assessed and recorded. Above all, the general physician's personnel must realize that they are working in the field of radiation and must be willing to accept a greater dose. It is quite possible that rules new but already in effect will require a marked increase in protective factors over the recent standards.

Laurence L. Robbins, Radiation hazards, *New England Journal of Medicine*, November 7, 1957, p. 926

The Significance of Nuchal Rigidity

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"If thou examinest a man having a gaping wound in his head, penetrating to the bone and perforating his skull; . . . shouldst thou find him unable to look at his two shoulders and his breast, and suffering with stiffness in his neck, . . ." The Edwin Smith Surgical Papyrus.[1]

THESE words, written by an unknown Egyptian scribe more than 4500 years ago, represent the first known mention of nuchal rigidity in the medical literature. The term "stiffness in his neck" actually appeared 17 times in this unfinished surgical treatise and in each case it was associated with an injury of the head or spinal column. The frequency with which this term was used makes it evident that even in the ancient Middle East it was recognized as a valuable diagnostic sign, one apparently reliable enough to color the prognosis offered by the physician.

MATTHEW W. WOOD

HENRY W. DODGE, JR.

Since the writer set his quill to this archaeologic epic, the face of medicine has changed a hundred times. In a broad sense, however, it has not changed at all. We, as doctors, are still expected to organize the signs and symptoms presented to us by a confident patient and to advance a plan for arriving at a diagnosis and instituting therapy. The correlation of the signs with the symptoms and their in-

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corporation into a feasible diagnosis constitute still the most important and, at times, the most difficult problem in medicine.

The signs and symptoms which are common to a myriad of disease entities are the easiest elicited and the least helpful in a differential diagnosis. On the other hand, there are those which, if present, immediately implicate the pathologic process involved. It should be kept in mind, however, that there are many signs and symptoms which are not specific for any one disease but which are limited enough in occurrence to be of great value to the attending physician in assaying a particular problem. Just such a medical facet is the presence of nuchal rigidity.

Definition

Nuchal rigidity or stiffness of the neck is best defined as the inability to produce cervical flexion, either actively or passively, without encountering resistance and causing pain and spasm. The amount of resistance, pain and spasm evoked on such motion varies, depending on the type and extent of the pathologic process involved. The stiffness may be minimal, unapparent to the patient, and elicited only on careful examination. On the other hand it may be quite severe, with complete resistance being offered to any slight movement of the head and neck. The rigidity affects in particular the extensor musculature of the neck, so that while flexion of the neck may be impossible, hyperextension is readily carried out. When this condition is marked, the patient more and more assumes the position of cervical hyperextension with retraction of the head. This may become so severe that even swallowing is impossible. Rarely, in severe cases of meningeal involvement, the patient may proceed to the opisthotonoid posture in which the extensor muscles of the neck, back and legs are rigidly contracted, resulting in an arched back supported by the occiput and the heels (figure 1).

Etiology

Nuchal rigidity is the most widely accepted and frequently encountered sign of meningeal irritation and is almost universally present in cases of meningitis. DeJong[2] has pointed out that the only instances in which it is not present in association with meningitis may be in fulminating or terminal cases or in disease of very young infants. However, it must be remembered that nuchal rigidity can occur in a number of diseases of diverse character and its presence may have either trivial or ominous connotations. It usually occurs as one symptom in a sequence of symptoms, appearing initially or developing subsequently in the course of a disease. The seriousness of nuchal rigidity is, of course, dependent on its cause.

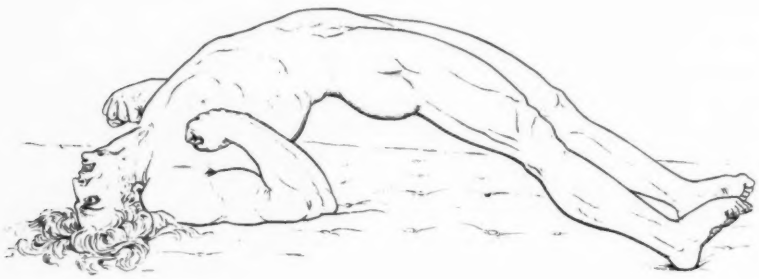


FIGURE 1. Patient in opisthotonos.

(From a drawing by Sir Charles Bell.)

Etiologic factors include the following:

I. Irritation of the basilar meninges
   A. Congenital
      1. Arnold-Chiari syndrome
      2. Leaking meningocele
   B. Traumatic
      1. Intracranial hemorrhage or infection secondary to trauma
   C. Inflammatory
      1. Meningitis
      2. Meningo-encephalitis
      3. Extradural or subdural abscess or empyema
   D. Masses
      1. Herniation of unci or cerebellar tonsils
      2. Tumors about the foramen magnum
      3. Rupture of cyst into the subarachnoid space
         a. Cyst of Rathke's pocket
         b. Sterile abscess
         c. Parasitic cyst
   E. Vascular
      1. Subarachnoid hemorrhage
      2. Intracerebral hemorrhage
      3. Extradural or subdural hemorrhage (hematoma)
   F. Allergic
      1. Postvaccinal encephalopathy
      2. Intrathecal injection of serum
      3. Foreign body (PANTOPAQUE®); other?
   G. Other
      1. After spinal puncture

II. Involvement of the cervical vertebrae
   A. Congenital
      1. Klippel-Feil syndrome
      2. Congenital hemivertebra
      3. Sprengel's deformity (especially bilateral involvement)
      4. Platybasia
   B. Traumatic
      1. Fracture of a vertebral body or the posterior elements of the vertebra
      2. Fracture-dislocation
      3. Dislocations of cervical portion of spinal column without fracture
      4. Whiplash injuries
      5. Protruded intervertebral disk
   C. Inflammatory
      1. Tuberculosis of cervical portion of spinal column
      2. Osteomyelitis of cervical portion of spinal column
      3. Postinfectious dislocation of C-1
      4. Specific arthritides (gout, psoriasis)
   D. Masses
      1. Benign
         a. Osteochondroma
         b. Hemangioma
         c. Giant osteoid-osteoma
         d. Aneurysmal bone cyst
      2. Malignant
         a. Osteogenic sarcoma
         b. Fibrosarcoma
         c. Multiple myeloma
         d. Metastatic lesions (especially from the breast, lung and kidneys)
   E. Vascular
      1. Hemangioma of the vertebra
   F. Degenerative
      1. Facet syndrome
      2. Degeneration of intervertebral disk with narrowing of interspace
      3. Hypertrophic arthritis
   G. Unknown
      1. Rheumatoid spondylitis

III. Involvement of soft tissues of neck
   A. Congenital
      1. Cyst of thyroglossal duct
      2. Cyst of branchial cleft
   B. Traumatic
      1. Contusion of cervical musculature
   C. Inflammatory
      1. Paravertebral infectious processes
         a. Quinsy
         b. Cervical adenitis
         c. Acute and chronic abscesses
         d. Other
      2. Poliomyelitis
      3. Epidemic myalgia (pleurodynia)
      4. Myositis
      5. Pneumonitis
   D. Masses
      1. Neoplasms of the neck excluding those of bony and intraspinal origin

E. Vascular
   1. Hematoma of the soft parts of the neck
F. Unknown
   1. Myotonia
   2. Scleroderma

IV. Involvement of central control of musculature
   A. Tetanus
   B. Extrapyramidal disease
      1. Parkinsonism
      2. Wilson's disease
      3. Torsion spasm
      4. Torticollis
   C. Unverricht's disease
   D. Anxiety tension states
   E. Alcoholism

Mechanism of Action

Generally speaking, spasm in the extensor muscles of the neck explains the presence of nuchal rigidity. However, the actual focus that initiates and perpetuates the muscular spasm often is not readily evident. The nuchal rigidity that occurs with most of the listed pathologic processes is logically explained. It is easy to imagine muscular spasm splinting the neck to avoid compression of a tender cervical node or to keep an extruded cervical disk from further impinging on a nerve root. It is most difficult, however, to explain such rigidity when it occurs with meningitis.

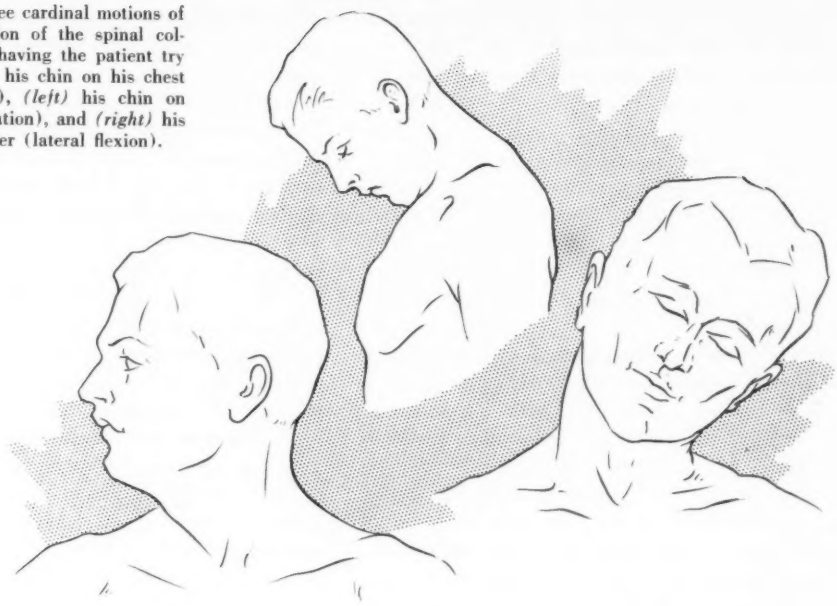
The opinions held on this subject are quite diverse. Neal, Jackson and Appelbaum[3] have expressed the view that the cervical rigidity seen in bacterial meningitis is due to hypertonicity of the muscles. Wilson[4] explained its occurrence on the basis of widespread muscular rigidity. Jelliffe and White[5] classed the muscular rigidity in meningitis under the heading of motor irritation and stated that it is often subject to considerable fluctuation, according to the degree of internal or external hydrocephalus.

Brain[6] expressed the belief that cervical rigidity is an example of reflex spasm of a protective character; when the neck is flexed, the motion raises the pressure in the cisterna magna and when the meninges are inflamed this is painful. Wechsler[7] supported the view that the rigidity is directly dependent on inflammation of the meninges at the base of the brain. O'Connell[8] advanced the hypothesis that nuchal rigidity, head retraction and leg signs seen in meningitis depend on the transmission of tension to inflamed and hypersensitive spinal nerve roots. He maintained that these signs are manifestations of postures designed to minimize tension in the inflamed roots, muscle spasm designed to limit movement productive of such tension, or movements designed to produce maximal relaxation in nerve roots rendered tense by some maneuver. Grinker[9] postulated that the extreme condition, opisthotonos, is caused by any disease in which material such as blood, pus or fluid distends the basal meninges, but he maintained that "its physiology is obscure."

Clinical Examination

When history taking evokes a symptom of nuchal rigidity, or a careful examination establishes its presence, it is then mandatory that the pathologic process underlying it be determined. The physician should ascertain whether an injury preceded the stiffness or whether it developed in the course of a disease. He should determine whether the stiffness is the only symptom or, if it is in a group of symptoms, where in the sequence it occurred. An exhaustive review of symptoms and a complete general physical examination are indispensable. Needless to say, an infection or mass anywhere in the body might be the clue needed to explain the nuchal rigidity. A careful examination of the ears, nose and throat should be made.

At the end of the general physical examination, special attention should be given to the upper extremities, head and neck. If possible, the cervical portion of the spinal column should be put through its range of motions and notation should be made of the time and site of the pain. The three cardinal movements of the cervical part of the spinal column, namely, flexion-extension, lateral flexion and rotation, should be attempted actively and passively. These motions can be assumed clinically if the patient is able to put his chin on his chest from full extension (flexion-extension),



IGURE 2. The three cardinal motions of he cervical portion of the spinal col-mn, elicited by having the patient try o place *(center)* his chin on his chest flexion-extension), *(left)* his chin on is shoulder (rotation), and *(right)* his ar on his shoulder (lateral flexion).

his chin on his shoulder (rotation), and his ear on his shoulder (lateral flexion), as illustrated in figure 2. It should be kept in mind that the chin can be placed on the shoulder without raising the shoulder, but the ear-on-shoulder motion cannot be carried out without doing so. These various postures should be attempted to the right and to the left in an effort to ascertain where the pain is produced. The ability to produce these movements will of course be limited by the severity of the pain produced. It is important to look for areas of point tenderness in both the soft tissues and the bony prominences of the neck. Special examinations, such as x-ray examination of the cervical portion of the spinal column and studies of the cerebrospinal fluid, should be carried out if indicated. Occasionally, only an exhaustive examination by a neurologist or orthopedist will uncover the underlying pathologic process.

Some idea of the severity of nuchal rigidity can be gained by observing the patient in bed. If the pathologic process is limited to his neck, the patient will lie with the cervical part of his spinal column immobile. He usually has found that he is more comfortable without a pillow, with the occiput flat on the mattress, or, if the rigidity is severe, he will have the pillow under his shoulders, with his neck extended. In torticollis and primary disease of muscle, the patient splints his neck in the position of comfort and turns his head insofar as muscle function allows. If meningeal irritation is the cause, he avoids lying on his side for fear of falling asleep and assuming a flexed position. He has found that extension can be maintained more easily if he lies on his back without a pillow. He avoids any flexion of his neck, and when rising from bed he will go to great lengths to insure poker extension of his cervical spinal column.

A simple test used for active determination of nuchal rigidity is to have the subject place his chin on his chest. This usually causes significant pain and spasm. To demonstrate this sign objectively, the examiner places his hand under the head of the recumbent patient. Gently, anterior and lateral flexion of the cervical spinal column is carried out until the patient complains of pain and the hand encounters resistance. Depending on where the head is,

in relation to the chest when the examiner elicits the pain and resistance, the nuchal rigidity can be divided into four grades. In grade 1 the symptoms develop just at full anterior or lateral flexion, when the chin approaches or touches the chest or shoulder. In grade 4 the examiner is totally unable to flex the cervical spinal column anteriorly, the patient resisting any attempt to lessen his 180° + extension of the neck. Grades 2 and 3 are increments between these two. This method of grading is of no value in determining cause or in ascertaining prognosis. Grade 4 stiffness of the neck does not necessarily carry with it a poor prognosis nor does grade 1 mean that the outlook is good. For example, grade 4 stiffness of the neck due to lymphocytic choriomeningitis has an excellent prognosis, while grade 1 stiffness of the neck due to a malignant tumor of the posterior fossa may carry with it a poor outlook. Nevertheless, grading is of value as a clinical yardstick in following the condition of a patient after the etiology of the nuchal rigidity has been determined.

It should be remembered that nuchal rigidity can vary considerably even in a 24 hour period and can disappear and reappear during the course of meningitis. Also, many bizarre forms of nuchal rigidity can be encountered in clinical medicine. It may simply take the form of a disproportion between the severity of pain elicited and the amount of muscle spasm and resistance produced; or it may be a quite unusual variant, unlike anything seen before. So-called lead-pipe nuchal rigidity, which was seen in a patient with alcoholism, is a good example of such a variant. In this particular case the examiner's hand produced pain and encountered spasm and resistance as soon as anterior cervical flexion was attempted. The spasm and resistance were uniform throughout the arc of flexion to the chin-on-chest position. If the examiner's hand was removed any time during flexion, the patient's head and neck stayed in the same position in which it was left instead of falling back into cervical extension. In order to get the head back on the examining table it was necessary to force it there by pressing on the patient's forehead, all the time encountering spasm and resistance. Such instances of bizarre nuchal rigidity are quite perplexing but they are of clinical interest.

A peculiar response is frequently seen in testing for nuchal rigidity in meningitis. It was originally described by Brudzinski[10] and consists of flexion of both thighs and legs on the pelvis when the patient's head is passively flexed on his chest. The test is carried out by placing one hand under the subject's head and forcibly flexing his neck while the other hand is placed on the chest to prevent elevation of the body. The sign is very common and is often present in early meningitis. In his original series, Brudzinski found this sign very rarely in other than meningeal disease—once in a case of encephalomyelitis and once in a case of mongolism. According to Wechsler[7] it occurs more often in tuberculous meningitis and is more easily elicited in younger children and infants than in older persons. He spoke of the sign as a Magnus and de Kleijn tonic neck reflex and did not believe that it is due to meningeal involvement. DeJong[2] agreed that it represents a tonic neck reflex in a partially decerebrate stage, but added that it might be a result of tension on the nerve roots. Grinker,[9] however, explained it on the basis of pressure, edema or vascular change caused by exudate in the interpeduncular space, which effects a physiologic break in the region caudal to the red nucleus and causes a release of lower tonus mechanisms. Brudzinski[10] himself pointed out that this sign is due neither to raised intracranial pressure nor to pain, but that it probably is caused in the same manner as Kernig's sign, according to the hypothesis of Chauffard; by muscular hypertonia in the lower extremities; and by a physiologic preponderance of the extensor muscles of the neck and back over the lower extremities.

Summary

Nuchal rigidity has long been recognized as an important diagnostic sign in clinical medicine. It is best defined as the inability to produce cervical flexion, either actively or passively, without encountering resistance and causing pain and spasm. The clinical findings elicited in a patient with stiff neck are de-

scribed and a method of grading nuchal rigidity is indicated. The primary cause for nuchal rigidity is extensor muscle spasm, but the exact mechanism initiating this spasm is often obscure. Its presence may have either trivial or ominous connotations, depending on the underlying pathologic process. An etiologic classification of nuchal rigidity is presented here.

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98. SCIATICA

In sciatica also there has been a tendency to over-stress the disc lesion, for although this often plays an important role in causation, the pain and tenderness depend upon changes which develop in the sheaths of the nerve roots which spread down the sciatic nerve and lead to great sensitivity to stretch as in straight leg raising. Alternatively, as in brachial neuritis, sciatic pain may be referred from muscles and ligaments near the spine or (in this case) the pelvic girdle. Measures designed to treat this abnormality of the nerve sheath should therefore often take priority. Rest in bed at the onset of the symptoms usually produces quick relief whilst the injection of lignocaine into the sciatic nerve or epidural space, or tender spots in the sacro-iliac region, may give dramatic relief. Plaster jackets are often helpful in stubborn cases but probably act chiefly by preventing flexion which pulls on the lumbosacral nerves when they are sensitive. There is no evidence that any form of non-surgical treatment will reduce the prolapsed disc.

W. Ritchie Russell, Advances in neurology, *Practitioner*, October 1957, p. 419

Benign Tumors of the Posterior Fossa

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AMONG the benign tumors that are seen in the posterior fossa are the cystic astrocytomas of the cerebellar hemispheres and the meningiomas that arise from the dura adjacent to the brain stem or overlying the cerebellum, coming down from the tentorium. Another small group consists of the so-called epidermoids or congenital type of lesions also known as cholesteatomas. The latter tend to arise in the midline, dorsally against the tentorium, or may occur in the angles. Finally, and this group perhaps constitutes the largest percentage of benign tumors of the posterior fossa, there are the neurinomas. The majority of these arise from the eighth nerve proper but they may also arise from the fifth nerve, occasionally from the tenth nerve, and from the accessory nerve (the latter only once in our experience). I am not including the tumors that involve many cranial nerves in association with Recklinghausen's disease or multiple neurofibromatosis.

All these lesions of the posterior fossa indicate their presence first by so-called local signs, depending on the area primarily involved. For example, cystic astrocytomas of the cerebellar hemisphere give rise early to cerebellar ataxia, dysdiadochokinesia, awkwardness of one side, difficulty in gait, and so forth. Later they may exert pressure on the underlying cranial nerves and then there are added signs due to involvement of the nerves of the cerebellopontile angle.

Meningiomas, depending on whether they arise from the ventral dura or from the dorsal portion of the cerebellar fossa and the tentori-

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tem, may indicate their presence first by nerve signs and later by cerebellar signs, or vice versa.

Similarly, epidermoids situated high and dorsal to the quadrigeminal plate may first give signs of local involvement of the eye muscle nerves with paralysis of upward gaze. Secondly the vermis cerebelli would be involved, with bilateral or truncal ataxia.

Neurinomas arise primarily from the eighth nerve itself, so we would expect auditory symptoms first, followed by signs of cerebellar involvement and, in all cases sooner or later, general signs of increased intracranial pressure. Symptoms such as headache, drowsiness, vomiting and impairment of vision occur when the tumor blocks the free flow of cerebrospinal fluid from the aqueduct and the fourth ventricle into the subarachnoid cisterns around the base of the brain.

If we remember that the posterior fossa is sharply circumscribed by the tentorium above and is pretty well filled by the cerebellum and the entire brain stem, it is not surprising that many of these tumors, though not extremely large, may cause general signs of increased pressure relatively early—far earlier, for example, than a tumor of similar size above the tentorium. You are all familiar with lesions of the anterior fossa such as frontal lobe tumors that may grow to tremendous size before signs of pressure develop.

Due to the very slow and insidious growth of these lesions of the posterior fossa, all too frequently their presence is not recognized until pressure signs do develop. This commonly means that despite successful surgical treatment there is irreversible damage from long-standing involvement of local or neighboring structures.

I am indebted to Drs. Joseph Evans and John Mullin of the University of Chicago for asking one of their patients to be here, and I want to thank the patient for coming. He is 58 years old and a most cooperative and intelligent person. His case demonstrates very well the problems that arise with respect to tumors of the eighth nerve, neurinomas, which constitute the bulk of the benign tumors of the posterior fossa.

(To the patient): According to the history I have, your first symptoms began three years ago, is that correct?

PATIENT: Approximately, yes.

DR. SCHWARTZ: What did you notice first?

PATIENT: Loss of hearing in the left ear.

DR. SCHWARTZ: Did it come on suddenly?

PATIENT: No, it crept up on me.

DR. SCHWARTZ: Do you recall any ringing in your ear at the time?

PATIENT: No.

DR. SCHWARTZ: Have you ever had any ringing in that ear?

PATIENT: I have never characterized it as ringing; it is a sort of pulsation or throbbing sensation.

DR. SCHWARTZ: This may fit under the general category of tinnitus, which is frequently observed in these cases. Did you have any attacks of dizziness, of vertigo? Did you feel the room spinning around about you?

PATIENT: No.

DR. SCHWARTZ: Did you have unsteadiness of gait?

PATIENT: That crept up gradually.

DR. SCHWARTZ: During the time when your hearing was getting progressively worse, did you seek medical attention?

PATIENT: Yes.

DR. SCHWARTZ: And you had a complete study, as I understand it, including x-rays, which were negative.

PATIENT: That is right.

DR. SCHWARTZ: Then there developed, in association with some unsteadiness of gait, some numbness of the face, is that correct?

PATIENT: Yes.

DR. SCHWARTZ: What did that feel like, can you tell us?

PATIENT: Well, just a numb feeling. I didn't lose control of the muscles. The numbness got progressively worse.

DR. SCHWARTZ: Did you have any difficulty chewing or swallowing or eating?

PATIENT: Just a little. At the beginning when I was chewing I would bite the inside of my cheek without feeling pain.

DR. SCHWARTZ: That is another symptom which we might consider due to loss of sensation of the trigeminal nerve and which is

a relatively common one in these conditions.

When the patient came to the University of Chicago Clinic, examination revealed diminished sensation over the entire distribution of the trigeminal nerve on the left. In addition, although he did not have peripheral facial paralysis, he did have loss of taste over the anterior two-thirds of the tongue on the left. It was also noted that he had deafness on the left, and the caloric response was absent on the left. Some nystagmus was observed on lateral gaze, there was some ataxia on walking, and Romberg's sign was present with a tendency to sway to the left.

This patient, then, had signs and symptoms referable to the fifth nerve, the sensory portion of the seventh nerve affecting his taste, and both divisions of the eighth nerve. The cochlear or hearing portion of the eighth nerve was affected, as evidenced by his deafness, and the vestibular responses were absent, as manifested by lack of labyrinthine responses on caloric testing. In addition there was evidence of left cerebellar involvement.

How can we put these findings together? Let us review the anatomy of the posterior fossa. The fifth nerve leaves the pons and rides over the petrous ridge to enter the middle fossa. Just caudal to the fifth nerve and about a centimeter behind it lies the eighth nerve. Tucked beneath the eighth nerve lies the seventh nerve. The seventh and eighth nerves go out together through the internal auditory canal. Lower down, the complex of the ninth, tenth and the spinal accessory nerves, the eleventh, approach each other to leave through the jugular foramen.

The patient presented had symptoms referable to the trigeminal nerve. He had symptoms referable to both the vestibular and cochlear divisions of the eighth nerve. He had some impairment of the sensory fibers of the facial nerve transmitting taste. He did not have involvement of the lower cranial nerves, but there were signs referable to the overlying cerebellar hemisphere.

A diagnosis of tumor of the cerebellopontile angle was made, and Dr. John Mullin did a perfectly beautiful piece of surgery, resulting in total removal of the lesion. At operation he found that the facial nerve was markedly stretched out, as it usually is, by the capsule of the tumor, and it was spared so far as its anatomic continuity was concerned. However, physiologically the facial nerve was paralyzed, and this happens in almost all instances of total removal of tumors of the eighth nerve, because of the size the lesions have reached when the neurosurgeon sees them.

The postoperative course was uncomplicated. A couple of weeks after craniotomy, a spinal accessory-facial nerve anastomosis was performed, and this is just beginning to function. The spinal accessory nerve fibers have been growing down into the distal part of the facial nerve, and in another few months I believe the patient will have complete symmetry of his face.

There are some residual findings. His eye movements are full but there is nystagmus on lateral gaze with a quick component to the left, the result of involvement of the cerebellar-vestibular pathways. He is unable to close his eyes; instead, he demonstrates the characteristic Bell phenomenon. In the presence of paralysis of the orbicularis oculi, the eyeball rotates upward to protect the pupil. There is residual hypalgesia of the trigeminal distribution on the left side, but this apparently has improved considerably since surgical treatment relieved the pressure on the trigeminal sensory root and, again, represents a good result. He has a very active corneal reflex. There is some depression of corneal sensation on the left side along with the rest of the trigeminal innervation. There is no evidence of any ataxia at present involving the upper extremities, and unless one looked very carefully I do not think one would say he has any disturbance of gait. When he turns rapidly to either side there is slight instability of gait, representing a residual of cerebellar involvement. He does extremely well considering that he has had some involvement of the cerebellum, and I would say that for practical purposes he has very little in the way of residual disability. He does have a facial palsy, which will be taken care of as soon as the accessory fibers reinnervate the facial nerve. That is done at the expense of some innervation of

the shoulder muscles; whether one uses the accessory or the hypoglossal nerve is a matter of personal choice.

Early diagnosis of these tumors of the cerebellopontile angle is exceedingly difficult. Remember, these are slow-growing lesions, they are benign, they take a long time to develop. Only if the physician has a very high index of suspicion can he recognize them at an early stage. When a patient complains of deafness, bear in mind the anatomic picture we have just reviewed and the usual sequence of symptoms and signs.

Since these tumors almost always arise from the vestibular portion of the eighth nerve, it is understandable that the earliest symptoms will be referred to the acoustic nerve, both its vestibular and its cochlear divisions. They may take the form of tinnitus, ringing in the ear, buzzing in the ear, first; or they may take the form of diminished hearing. In some cases vertiginous attacks may occur that are not too different from those seen in Meniere's disease. In any event, the initial symptoms are inevitably acoustic and occur very early.

It is extremely interesting that the next most frequent early symptom is involvement of the trigeminal nerve. This may manifest itself merely as a depression of the corneal reflex. The sensory root of the trigeminal nerve lies about a centimeter ahead of the eighth nerve. These tumors tend to spread along the path of least resistance, and they impinge on the trigeminal nerve, which is very vulnerable to pressure, causing the early appearance of trigeminal symptoms.

Headaches also occur early. They are not the type seen in association with general increased intracranial pressure but are more likely due to some tension on the dura by the tumor or to tension on the trigeminal nerve, which reflects itself in headache referred either to the frontal region or to the vertex.

Next in order are cerebellar symptoms. As the tumor grows and expands dorsally, it begins to press against the cerebellum and embarrass the circulation of the cerebellar nuclei. Later, double vision develops. It may be due to rotation of the entire brain stem, including the upper portion of the mesencephalon, which may cause traction on the fourth and sixth nerves, or it may be due to the onset of generalized increased intracranial pressure with compression of the third nerve at the tentorium.

Surprisingly, symptoms referable to the facial nerve are relatively uncommon or occur relatively late. This has always seemed remarkable to me, considering that the facial nerve and the eighth nerve go out side by side in the internal auditory canal and at operation we always find that the facial nerve is tremendously distorted, stretched out, obviously under marked tension by the capsule of the tumor. This suggests that the facial nerve can tolerate slow compression for a longer period than can the trigeminal nerve.

Finally, as the tumor continues its course along the path of least resistance and begins to grow downward along the brain stem, it impinges on the ninth, tenth and eleventh nerves, and then the patient has difficulty in swallowing.

Careful audiometric examination and caloric testing of every patient who complains of hearing loss may lead to early recognition of these tumors. The hearing tests should include not only the routine audiometric study but also tests for speech discrimination such as the Rush-Hughes test. Walsh and Goodman of our department of otolaryngology have demonstrated clearly that in many of these early cases, due to central involvement of the eighth nerve, the threshold for pure tones may be relatively unimpaired but loss of speech discrimination is present in a far greater degree than is the pure tone loss.

We have also found it very desirable to repeat audiometric and caloric tests and to make very quick neurologic surveys in any patient who continues to complain of progressive deafness which cannot be explained by some other obvious condition. Only by repeated testing may we be able to recognize these tumors as they continue to develop, and before they reach so tremendous a size that any chance of saving the brain stem or the facial nerve is gone.

I also think that x-rays should be made of every patient who complains of deafness. In

the case described, x-rays were made when this patient first sought medical attention and the films were normal; they were also normal when he came to the University of Chicago Clinic. My reason for stressing x-rays, however, is the fact that in about 30 per cent of these cases they will show erosion of the internal auditory canal.

When a tumor is suspected, the cerebrospinal fluid should be examined. In many instances the level of protein is elevated. Air studies may be necessary at times in order to delineate the region of the cisterna pontocerebellaris.

We have had experience with three rare instances of bilateral acoustic neuromas in young women without any evidence of multiple neurofibromatosis. In these bilateral cases, deficits of facial nerves are particularly appalling and hearing loss is total.

I believe that with careful otologic examination, particularly caloric and speech discrimination tests, plus a very high index of suspicion, it may be possible to recognize these tumors very early, before they reach a tremendous size. This may give us an opportunity to spare not only the facial nerve but also (in rare cases) the cochlear division of the eighth nerve and thus preserve some useful hearing.

Postgraduate Clinical NOTES

99. RAYNAUD'S PHENOMENON

A Raynaud's phenomenon which has been present for many years is almost certainly primary, and absence of trophic changes confirms this. Although primary Raynaud's phenomenon usually starts in childhood, it may not do so and may be seen for the first time later in life, although usually in such patients there is a previous history of chilblains or acrocyanosis suggesting a tendency to undue reaction to cold. Trophic changes mean digital artery obstruction and are important evidence of occlusive disease. Symptoms of scleroderma—stiffness or thickening of the skin of the fingers or face, or dysphagia—may be present when the circulatory changes start, and indicate this disease, but as a rule arterial changes antedate these, often by some years. In a man, and rarely in a woman, arterial insufficiency elsewhere, or recurrent superficial phlebitis, would suggest thromboangiitis as the cause of the symptoms.

The diagnosis between the late onset of a primary Raynaud's phenomenon and the early onset of a Raynaud's phenomenon secondary to scleroderma is often difficult or impossible without a digital arteriogram or without observation of the patient for a year or more. In most patients with primary Raynaud's phenomenon a digital pulse can be felt when the patient is really warm, but in those with secondary Raynaud's phenomenon this is never so. Rheumatoid arthritis or rheumatic fever is sometimes responsible for the symptoms, or there may be a history of injury, frostbite or the use of vibrating tools. Cold haemagglutinins may be detected in the blood occasionally and would indicate the diagnosis.

Peter Martin, Raynaud's phenomenon, *The Practitioner*, August 1956, pp. 176-183

DIAGNOSTIC CLINIC

Carcinoma of the Breast

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CARCINOMA of the breast is an extremely frequent disease. It is the most common type of cancer in women, feared by all and ultimately developing in about 4 per cent of the female population. About 16,000 deaths from breast cancer occur each year in the United States, with only a very small incidence among men.

WALTER G. MADDOCK

A lump in the breast is the most common presenting symptom of breast carcinoma. Although pain is also a common symptom, it is associated usually with chronic cystic involution. It is important to remember that an axillary mass occurs in a much higher percentage of cases than is presumed. An additional disturbing feature is that 60 per cent of patients already have axillary metastases by the time they consult a physician. A nodule approximately 1 cm. in size is about the smallest lesion that one can detect by palpation. Patients in whom nodules of this size are seen usually can be cured, although it is true that, occasionally, even these small lesions metastasize; generally, the larger the lesion and the longer it has been present, the more widespread the disease process.

The treatment of carcinoma of the breast is becoming progressively more difficult. When we relied primarily on radical mastectomy alone and x-ray postoperatively or for recurrence, the treatment was relatively simple. Now, there are many decisions to make in dealing with this lesion. Our entire effort in regard to treatment is directed toward seeing the patients early in the course of the disease and doing the definitive treatment at a time when we can hope to cure the disease.

Although there has been some question regarding the value of therapy in cancer of the breast, there is no doubt that it is necessary and beneficial. A study of the five year life expectancy of persons in a similar age group with and without carcinoma of the breast revealed that 94 per cent of those who do not

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have breast cancer live five years. The over-all survival rate for those who have cancer and who have radical mastectomy is 50 per cent; 74.5 per cent of those who have radical mastectomy with the disease limited to the breast survive, while only 40 per cent survive when axillary nodes are involved. These figures become increasingly important when one considers that of 100 persons who have untreated operable carcinoma, only 19 per cent are alive in five years.

In all discussions of breast cancer, the names of William Halsted of Baltimore and Willy Meyer of New York are outstanding. The operation which they developed for carcinoma of the breast is much the same as that which we use at the present time. Dr. Halsted was a very interesting gentleman. During his career at Johns Hopkins, he concentrated on research rather than on surgery. He was interested in problems and in their solutions. He tried the supraradical operation for carcinoma of the breast, but abandoned it because it added nothing to his patients' survival time.

Radical Mastectomy

In the routine radical mastectomy, the breast and almost the entire underlying pectoralis major muscle and the pectoralis minor muscle are removed. It is necessary to do a meticulous axillary lymph node dissection. This whole operation usually requires from two to three hours. Although some surgeons use twice this length of time for the operation, I do not think much is gained by the longer period. However, it has been convincingly demonstrated that the better the operation, the better the five year results. A study conducted at Presbyterian Hospital, Chicago, in which the radical breast specimen was carefully cleared and every lymph node of the axilla was found, plotted and studied for metastases, showed conclusively that the surgeons whose dissections removed the greatest number of axillary lymph nodes generally had the highest five year survival rate. There is some hope for even the worst cases.

Harrington of the Mayo Clinic, who probably had more experience with radical mastectomy than anyone else in the world, reported a survival rate of 12.5 per cent in 10 years and 8.2 per cent in 15 years in patients who had axillary metastases and grade 4 lesions, which are the most serious.

I would like to emphasize that although we frequently speak of a five year survival rate, unless the figures are broken down further, those patients to whom we refer as surviving for five years may be living and well or they may be living with cancer.

At the Henry Ford Hospital, a study on the first recurrence in a group of 48 cases showed that in 20 patients, the cancer recurred in less than five years; in 20, it recurred in from five to nine years; in six, there was recurrence in from 10 to 14 years, and in two, it recurred after 15 years. Most physicians are aware of this strange long period before breast cancer reappears in some patients.

Bleeding From the Nipple

Bleeding from the nipple is a surgical problem. In studying a series of cases, Campbell reported the following causes of such bleeding: intraductal papillomas in 35 per cent; chronic cystic involution in 25 per cent; and carcinoma of the breast in 40 per cent. Bleeding from the nipple caused by a cancer which is not palpable is extremely rare. In other words, if there is bleeding from the nipple due to cancer, almost invariably that cancer is palpable.

The examination procedure in cases of bleeding from the nipple is to carefully palpate the breast, particularly in the area of the areola in order to see from what duct one can force blood. It then is necessary (1) to dissect a duct for an intraductal papilloma, (2) to remove a gross carcinoma, or, more rarely, (3) to excise a wedge-shaped section of breast because of chronic cystic involution. The pathologist will determine whether or not carcinoma is present.

I condemn the procedure of trying to put a needle through a nipple duct from which blood is coming. Preoperatively, a patient does not appreciate this sort of investigation; in addition, the procedure is not helpful. By pressing around the areola, one can usually find from which duct the blood is coming. By a circum-

areolar incision around this position, one can develop the duct involved; in a high percentage of cases, it is easy to find an intraductal papilloma that is the cause of the bleeding. Of course, it should be examined microscopically. If a papilloma is palpable preoperatively, it probably is malignant. If it is not palpable preoperatively, there is a very good chance that it is a benign tumor. I have yet to see a patient in whom the papilloma could not be found by careful dissection at operation.

If the bleeding or serosanguineous fluid discharge is so slight or so infrequent that one cannot locate from which duct it is coming, it is safe to observe these patients, because, as previously stated, if the bleeding is due to cancer, that cancer will be a palpable one. Rarely is a mastectomy indicated for unaccountable breast bleeding.

Chronic Cystic Involution

The relation of chronic cystic involution of the breast to carcinoma of the breast has been a debatable question. Warren distinctly believes that the former is a precancerous lesion; however, the majority of investigators in this country do not agree with this theory. Warren examined a series of cases from Toronto and Boston and concluded that carcinoma of the breast was 4.5 times more common in the entire group if chronic cystic involution was present. In patients more than 50 years of age, the incidence of cancer was 2.5 times more frequent; in the 30 to 49 year old patients, cancer was 11.7 times more common. In my experience, on clinical examination almost all women patients show some degree of chronic cystic involution. I doubt that it is proper to relate one to the other in a cause-and-effect sequela. I rarely do a radical mastectomy on a breast showing the scars of previous operations for chronic cystic involution. It is interesting that although Warren rates the latter as precancerous, his recommended treatment is no different than one would utilize in following the rule of excising all tumors of the breast when found. A few authorities believe that when tissue of chronic involution shows very marked intraductal hyperplasia, a simple mastectomy should be done. Others advise re-examining these patients every three to four months, as one should do in all patients with chronic cystic involution who have symptoms.

Hormone Therapy

Hormone therapy, using androgens and estrogens, is part of the armamentarium for dealing with recurrent carcinoma of the breast. Subjective improvement has been noted in patients receiving these substances. However, hormone therapy may cause side effects of dyspnea, edema, nausea, headache and anorexia. Edema may bring on cardiac failure in patients who are close to a loss of cardiac reserve. Hypercalcemia may also occur in these patients. It is necessary to watch for this condition, and if it occurs to prescribe a low-calcium diet.

Patients sometimes object to hormone therapy, particularly to the use of androgens, because of their masculinizing effect. The resulting hirsutism is most distressing; lowering of the voice, acne, etc. may occur. For these reasons, some patients will not continue hormone treatment. I had a patient who was concerned because of embarrassing incidents due to the lowering of her voice; another patient (the elderly wife of a bishop) would not continue treatment after she noted increased libido.

The objective improvements are fairly good with hormone therapy. The soft tissues improve in a fair number; skin metastases shrink with both substances, and pleural metastases often lessen. Liver metastases do not improve with the use of estrogens, but there seems to be some reduction in size with the use of androgens.

Certainly, hormone therapy should be given a trial in patients who have recurrent carcinoma, as it has proved to be a good standard treatment. Patients may be treated for from a number of months to over a year with relatively small oral doses. The common consensus in this regard is to use the androgens for menopausal or up to five years postmenopausal patients, and to use the estrogens for those five years plus. I believe that the low price which the majority of patients pay for hormone therapy is compensated by the sim-

plicity of the treatment, compared with other forms of therapy, and by the life-extending benefits of the hormones.

Oophorectomy

The question of the advisability of oophorectomy is a difficult one. A bilateral oophorectomy removes the major source of endogenous estrogens and often affects the course of recurrent breast carcinoma. Remissions of about nine months will occur in about half the patients. In patients who do not respond favorably (and it is very difficult to tell which patient will and which will not), androgens are given a trial. If initial improvement after oophorectomy relapses, adrenalectomy should be considered; this gives another nine months of relief in about half the cases.

For menopausal patients and for those up to 10 years postmenopausal, a bilateral oophorectomy and adrenalectomy will give a 10 month remission in about 60 per cent of the cases. With the patients showing no response, androgen therapy or hypophysectomy will not give much improvement. In 12 such attempts there was only one remission. Estrogens are used in the patients who are more than 10 years postmenopausal; about half of them will show some remission. When there is a recurrence of the growth of the tumor, the next step is the use of androgens or a hypophysectomy. For those patients who do not respond to estrogens, adrenalectomy should be considered.

Hypophysectomy

Some investigators are trying hypophysectomy as the immediate treatment for recurrent carcinoma of the breast. As far as substitution therapy is concerned, patients are easier to control after hypophysectomy than after a bilateral adrenalectomy. A study of hypophysectomy made by Bronson Ray, which probably reflects the greatest experience in this country, shows that in 56 patients who were postmenopausal there were remissions in 28, failures in 24, and four were unevaluated. These remissions lasted almost a year before there was a return of tumor activity, and the patients were much improved generally. In 38 patients who had had spontaneous menopause, there were remissions in 20, failures in 16, and two were unevaluated. In 18 patients who had had induced menopause by a previous oophorectomy, there were remissions in eight, failures in eight, and two were unevaluated. In eight premenopausal patients, there were two arrests, three regressions and three failures.

Hypophysectomy might appear to be quite a formidable procedure, but in the hands of a neurosurgeon it is not too difficult. One of the problems is the necessity of removing *all* the pituitary gland. In autopsies on some patients who had had this treatment, unfortunately, a small remnant of the pituitary had been left. Hypophysectomy has been tried by external and local applications of radiation therapy.

Cortisone

Cortisone seems to be somewhat effective in producing remissions. A study showed that in doses of 200 to 400 mg. per day, it effected remissions averaging three months in 30 per cent of patients. The improvements were seen in both hormone-dependent and nonhormone-dependent tumors. The reason for the result is not definitely known.

Discussion of Representative Cases

There are three patients here today whose cases illustrate specific problems. The first patient, a 38 year old woman, was admitted to the hospital with a mass in the right breast. A nodule in the breast, which had been diagnosed as chronic cystic involution, had been watched for two or three years. It grew larger, and the patient came in for treatment. She had been menstruating regularly every 28 days.

At the time of our examination, the mass was 3 by 3 cm., just under the right areola. The axillary nodes were about twice normal size. The skin over the mass showed some dimpling, but the tumor was not fixed to the underlying tissues. The laboratory studies were not remarkable.

A radical mastectomy was done and a poorly differentiated scirrhous adenocarcinoma, with metastases to the axilla, was found. Her chest wound is healing very nicely.

At this point, I would like to interject an explanation of my method of keeping a firm compression on these wounds postoperatively. It is difficult to get just the right compression on the skin flaps without having it too tight. Multiple adhesive straps with hooks to which rubber bands are attached produce even pressure and reduce the amount of fluid collecting under the flaps. If some fluid does collect, the incision is opened a bit and a small drain is inserted. If the drain is not used, the fluid collects again.

Another valuable experience I would like to describe is in relation to handling small areas of necrosis in the skin flaps. Should a dark area, perhaps 1 in. wide and 3 or 4 in. long, develop by the third or fourth postoperative day, one can trim out this necrotic area and resuture the flaps right away; it will heal very nicely, which would seem to be unusual. One would suspect that the sloughing resulted from a skin flap which was too tight. Therefore, you would assume that cutting out a strip 1 in. wide and resuturing the wound would increase the pressure and thus produce more sloughing; however, such just does not seem to be the case. I have never seen a second slough occur after trimming and resuturing.

In the case of this patient here today, the question now is whether or not to do an oophorectomy. We think that because of the marked axillary node involvement in this premenopausal woman a bilateral oophorectomy will be of some advantage. Ordinarily, this procedure is reserved for recurrence, but in this case, it may be a factor in preventing or delaying possible recurrence.

Another interesting case is that of a 54 year old woman who is two years postmenopausal and whose radical mastectomy specimen revealed completely involved axillary lymph nodes. At the present time, the patient shows no evidence of recurrent disease. The question of further therapy gave rise to the opinion that if she showed evidence of active estrogen production at a sufficient level to produce cornified vaginal mucosa and cornified cells in a vaginal smear (that is, a number more than just an occasional cell), she would obtain benefit from surgical oophorectomy or ovarian radiation at the present time. The preference is for surgical oophorectomy, since it is thought that the removal of the major source of estrogen would be both quicker and more certain by this means. This patient's vaginal smear did not show cornified cells; consequently, an oophorectomy was not advised. You must realize that these are all somewhat experimental procedures; it is going to take time to determine their proper place in treatment so that they might be used to achieve the best results for the patients.

The next patient came in with thickening of the skin in the left armpit. She had had a right radical mastectomy for carcinoma in 1945. A course of postoperative radiation therapy immediately followed. The patient has had frequent checkups since that time. During the four months prior to this last hospitalization, she had noticed increased thickening of the left axilla, and she had had some vague pain. She is 10 years postmenopausal.

Examination revealed no tumor in the left breast and a well-healed right radical mastectomy scar, but there was some thickening in the left axilla. Since bone studies revealed no signs of metastases, it was decided to do a left radical mastectomy.

The pathology report for the left breast revealed no carcinoma, but abnormal cystic involution and slight sclerosing fibroadenomatosis were present. The left axillary lymph nodes showed poorly differentiated scirrhous carcinoma in 16 or 17 sections, which was the same condition as that found in the right breast 10 years previously.

Of course, the patient now has the bilateral scars; they are well healed. There is no sign of recurrence on the right side, but there is a moderate edema of the left arm. She has a good range of arm motion. The axilla is clear on the right side. She feels exceedingly well. The x-rays of the spine, pelvis, skull, etc. are completely negative. I know of no other malignant areas. At present, I plan to wait to use the armamentarium that I have mentioned, i.e., hormones, x-ray, adrenalectomy and hypophysectomy, and consider them only if there are signs of recurrence.

The third patient is 60 years old. She came

to the hospital with the chief complaint of dimpling of the skin of the left breast. At the time of admission, she had a 2 by 2 cm., firm and poorly circumscribed mass just lateral to the left nipple. The skin was retracted and showed some fixation. A diagnosis of carcinoma of the breast was made, and a radical mastectomy was done. It showed involvement of the lymph nodes in one of seven sections. After the operation, the patient was discharged on November 8, 1954. She was readmitted to the hospital on May 5, 1957, approximately two and a half years later, with pain in the left shoulder. Following the left radical mastectomy, she had been in good health until six months before readmission to the hospital. She always had had a mild pain in the left shoulder and arm, but this had become much worse. The essential thing was that the right breast showed nontender fixed nodules 3 by 5 mm. in diameter in the skin close to the sternal border. There was no breast tissue tumor palpable. The right axilla felt normal. The left arm revealed an anesthetic area over the innervation of T11, and there was some paresthesia around the side. X-rays of the skull demonstrated the presence of rounded and irregular areas of radiolucency. X-rays of the ribs, cervical spine and lumbar pelvis revealed extensive osteolytic lesions.

Tests on the patient revealed increased amounts of serum and urinary calcium excretion, which were in keeping with the finding of osteolytic lesions. A hypophysectomy was done about four months ago. As you can see, the patient now looks extremely well. The pelvic and arm pain has been considerably relieved; the patient is active and notices no bad effects from the hypophysectomy.

This is an experimental treatment; there was nothing else to do for this patient. The substitution therapy has been easy, and we have a good result. Unfortunately, not all results are the same; however, 50 per cent of such cases show improvement for from a few months up to a year and a half.

Gout and Collagen Disease

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In this discussion I shall consider the problem of arthritis in relation to two of the less common types of joint disease. In order to illustrate the natural history of each disease and to point out specific and general phases of treatment, I would like to present two patients. The first, Mr. S., has gout; he is 59 years old.

When did you first have trouble with your joints, Mr. S.?

PATIENT: About 25 years ago.

DR. TALBOTT: In retrospect, was that the first evidence you had of any clinical manifestation of gout?

PATIENT: I think so.

DR. TALBOTT: Have you ever had any symptoms other than joint disease which were related to uric acid disturbance?

PATIENT: I had kidney stones before that.

DR. TALBOTT: Mr. S. had his first kidney stone 10 years before his first attack of gouty arthritis. This is significant, for from 15 to 18 per cent of patients with gout have a history of kidney stones. When we use a uricosuric agent in therapy, it is important to know whether or not we are aggravating the tendency toward the formation of uric acid stones. The answer is negative.

Mr. S., about how many kidney stones have you passed in the last 35 years?

PATIENT: Between 25 and 30.

DR. TALBOTT: In my experience, the occurrence of 25 stones in 35 years constitutes a record.

PATIENT: I had two removed by surgery.

DR. TALBOTT: It is interesting to know that surgical intervention was necessary on two occasions. About how many cystoscopic examinations have you had?

PATIENT: At least 15.

DR. TALBOTT: For the past seven and one-half years, you have been taking BENEMID®

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and colchicine. Have you had as much trouble with kidney stones during this time as you had before therapy was started?

PATIENT: It has been about the same.

DR. TALBOTT: The fact that the incidence of stones has been similar, irrespective of the use of Benemid, is in keeping with our theoretical concept of the disease.

From your history, Mr. S., it is evident that the joint disease did not cause you too much trouble during the first few years that you had it. In fact, is it not correct that when you were inducted into the army in 1941 you did not even mention that you had gouty arthritis?

PATIENT: That is correct.

DR. TALBOTT: But you did have some trouble from gout while you were in the service?

PATIENT: Yes. After several years, I had a very bad knee. The doctors thought it was an infection because it was so swollen.

DR. TALBOTT: This is a significant development. In gouty arthritis when the great toe becomes involved, it is sometimes suspected of being a septic joint and is not properly diagnosed. In this instance, the possibility of septic arthritis was entertained because of the large effusion of the left knee. Not until the knee was aspirated and the culture found sterile was gouty arthritis considered as an explanation for the acute attack. As a result of this, the patient was released from the army in 1944.

Mr. S., from 1944 to 1948, was there any change in the incidence of acute gouty arthritis attacks?

PATIENT: Yes. The attacks increased in number.

DR. TALBOTT: Prior to 1947, when we first started treatment, how many workdays per year did you lose?

PATIENT: I would say an average of about 20, in periods of three or four days at a time.

DR. TALBOTT: According to your history, subcutaneous tophi and tophi in your ears and feet were developing. Will you tell us why you consulted an orthopedic surgeon during this period?

PATIENT: The great toe on my left foot became so large that I had to take a slipper with me whenever I left home. It would become so swollen that I could not keep my shoe on after about two hours. I finally had the toe removed.

DR. TALBOTT: A picture of the foot before the toe was removed revealed that the urate destruction throughout the metatarsal phalangeal joint was such that the patient had a flail toe. Although I was not responsible for recommending removal of the toe, I heartily concurred with this procedure in retrospect. However, at the present time, we do not have to resort to surgery or to amputation because of extensive tophaceous deposits in patients who have gout.

There is a great deal in the literature regarding dietary control in gout. Would you tell us of your experience with this, Mr. S.?

PATIENT: I have tried several diets. At one time, I was on a meat-free diet for an entire year; however, it made no difference in the incidence of my attacks.

DR. TALBOTT: Have you submitted to such a rigid dietary restriction since 1948?

PATIENT: I eat anything I want to eat; I have no restrictions.

DR. TALBOTT: Do you abstain from the use of alcoholic beverages?

PATIENT: No. I would say that I am a normal consumer.

DR. TALBOTT: I am not quite sure of just what a normal consumer is; however, I would suppose that it means that in the evenings, at least, you indulge in alcoholic beverages when the opportunity to enjoy such extracurricular activity presents itself.

In 1948 or 1949, when Mr. S. was having a great deal of trouble with periodic attacks of acute gouty arthritis with resulting incapacity, I prescribed Benemid and colchicine, a regimen which he has carried on ever since that time.

How many Benemid tablets do you take a day, Mr. S.?

PATIENT: I have been taking three to four tablets every day since 1949.

DR. TALBOTT: During this period, have you detected any undesirable side effects caused by the drug?

PATIENT: No, not as such.

DR. TALBOTT: Since one tablet contains 0.5 gm. Benemid, three tablets would be 1.5 gm.

and four tablets would be 2 gm. a day. How much do you weigh?

PATIENT: About 170 lb.

DR. TALBOTT: Three to four Benemid tablets daily is about the average dosage for patients who weigh 160 to 180 lb. Patients who weigh 125 to 130 lb. may take two tablets each day.

Mr. S. is on continuous Benemid therapy because of his long history of over 25 years of acute gouty arthritis. He has obvious tophaceous changes in the subcutaneous tissues and well-developed changes evident through x-ray examination.

The action of Benemid is related to an increased excretion of uric acid from the body. Benemid, per se, has no effect on joint distress; however, it prevents further deposition of uric acid in the joints. Thus, its long-term effect is gradually to remove the uric acid from the joints, and, secondarily, to affect the incidence of acute attacks.

As I have stated, I also prescribed colchicine for Mr. S. at the beginning of the treatment. Colchicine has been available for more than six centuries; it is the only specific antarthritic drug we have. However, we still do not know why it works; we do not know its pharmacologic action; we simply know that it does work. Colchicine is of value in the treatment of acute attacks of gouty arthritis; it has no effect in any other joint disease.

What was the dosage of colchicine that I prescribed for you about seven or eight years ago, Mr. S.?

PATIENT: I started taking one tablet a day regularly.

DR. TALBOTT: Although this is the dosage which I usually prescribe, I think that I probably was a little remiss in not recommending that a patient who had this degree of gouty arthritis take at least two 0.5 or 0.6 mg. (1/100 or 1/120 gr.) tablets of colchicine daily. Mr. S. took colchicine daily for several years. What is your present intake of colchicine, Mr. S.?

PATIENT: I take it now only when I feel a twinge of pain which I know is the beginning of an acute attack.

DR. TALBOTT: How often is it necessary?

PATIENT: About every three or four weeks.

DR. TALBOTT: At what time of the day do you usually feel this twinge of pain?

PATIENT: Curiously enough, it occurs about 2 or 3 A.M.

DR. TALBOTT: Sydenham described the occurrence of such pain in the middle of the night also. How do you regulate the dosage of colchicine when the distress first appears?

PATIENT: I usually take two tablets when I feel the first twinge, two when I get up in the morning, and probably two at noon of that same day. They almost always stop the attack.

DR. TALBOTT: Have you lost any workdays because of attacks of gout since you started this therapy?

PATIENT: Not a single day during the last eight years.

DR. TALBOTT: There are several other features of this disease which I would like to emphasize. Mr. S., are there any other members of your family who have the disease?

PATIENT: My father and my brother had it very badly.

DR. TALBOTT: This is typical of the history obtained in the majority of patients whose relatives we are able to trace. However, such a history must be sought diligently, for, frequently, when we see a patient during the first attack of undiagnosed acute arthritis, we are not sure whether we are dealing with gouty arthritis, rheumatoid arthritis or acute rheumatic fever. If we elicit a positive family history of gout, particularly if it is in a male member of the family, we have further ancillary evidence that we are dealing with gouty arthritis.

It also is important to make periodic uric acid tests on the children of a patient with gouty arthritis. In the case of Mr. S., we have made tests on his 32 year old son and on his two daughters. The son has had an elevated uric acid concentration; however, the daughters' tests have shown normal levels. While the incidence of gout is about 20 times more prevalent in men than in women, we occasionally see a female patient with gout, and, of course, we cannot overlook the possibility of the development of gout in a female member of a gouty patient's family. Thus, in all chil-

dren of gouty patients, I determine the uric acid concentration once a year or so, depending on whether or not it is elevated.

In determining the uric acid level, serum, not whole blood, is used, just as in the determination of calcium, phosphorus, sodium, etc. The normal level is less than 5 mg.; the level of most gouty patients is greater than 6 mg. The concentration in Mr. S. was as high as 11 or 12 mg. before he started taking Benemid. With Benemid therapy, the depression is about 30 or 40 per cent and the level is around 6 or 7 mg. In fact, the last determination which was made was only 5 mg., which was due to the effect of Benemid. The escape from Benemid is a rapid one, occurring within 24 or 36 hours. If Benemid is omitted for a period of time, the levels return to the same value as before Benemid was administered. Therefore, when using Benemid as a uricosuric agent, it is necessary to maintain ingestion regularly.

The incidence of albuminuria is significant. You have had some albumin in your urine for a long period of time, have you not, Mr. S.?

PATIENT: Yes. I've had a slight trace.

DR. TALBOTT: It is most important to know the prognosis if albumin is present. Albuminuria, unexplained or without an associated diagnosis of gouty arthritis, may carry with it a different diagnostic implication. I have never seen a patient with albuminuria, per se, associated with gout who has the same serious trouble as that which results when albuminuria is associated with chronic glomerulonephritis.

I have several patients more than 70 and even 80 years of age who have been taking Benemid for periods ranging between four and six years. The effect of this drug is the same, irrespective of the age of the patient or of the presence of mild or moderate renal impairment.

Mr. S. has had obvious kidney trouble for many years, yet the action of Benemid has been thoroughly satisfactory; by taking a few tablets of this drug daily, he has been able to lead a perfectly normal life. The fact that he has not had an acute attack during the past eight years is related to his regular ingestion of colchicine prophylactically when he feels the first twinge of pain. Such a procedure has prevented the mild attack from becoming a severe one. Even patients who take Benemid and colchicine regularly usually have more trouble than Mr. S. has had.

There is one other important phase of therapy in this condition. It must be stressed that in dealing with uric acid, which has a low solubility in body fluids, it is necessary and vital that the fluid output be maintained with an increased fluid intake. Mr. S. makes a special point of taking a large amount of fluid every day.

Do you restrict your physical activity in any way, Mr. S.?

PATIENT: No. Temperatures—heat and cold—seem to make no difference.

DR. TALBOTT: And you are able to participate in sports such as hunting and fishing?

PATIENT: Yes. I can ride, go duck hunting in the cold weather, and take part in winter sports with no trouble at all.

DR. TALBOTT: So you are now able to live a normal life as a gentleman farmer without any problem whatsoever. Thank you very much, Mr. S.

The second patient whom I would like to present is Mrs. B. She has another type of joint disease in which the process has been chronic for a long period of time. Specific recommendations concerning treatment have done a great deal in her rehabilitation, permitting her to be here today to tell us her own story.

In what year did the onset of joint disease occur, Mrs. B.?

PATIENT: About 1951.

DR. TALBOTT: How old were you then?

PATIENT: Twenty-four.

DR. TALBOTT: In what part of your body did the trouble begin?

PATIENT: In my hands and fingers.

DR. TALBOTT: I presume that the diagnosis of specific arthritis was made at that time. It should be noted that we are not satisfied with the diagnosis of arthritis without an accompanying descriptive term. What type of arthritis did you have?

PATIENT: It was originally diagnosed as rheumatoid arthritis.

DR. TALBOTT: Between 1951 and 1956, the symptoms in this case did seem to indicate rheumatoid arthritis. The changes in Mrs. B.'s hands, essentially symmetrical in both hands, are typical of well-developed rheumatoid arthritis. During the course of her illness, there have been times when she could not close her hands to make a fist.

Have any nodules appeared during your illness, Mrs. B.?

PATIENT: Just once; early in 1954, one appeared on the back of my right knee.

DR. TALBOTT: Occasionally we see rheumatic nodules. When they occur, they usually are in proximity to the affected joints, the large joints, or the smaller joints of the hands or feet.

After the diagnosis of rheumatoid arthritis was established, Mrs. B., what specific drugs were recommended during the first five years of the disease?

PATIENT: I first took cortisone and ACTH.

DR. TALBOTT: Were these agents beneficial?

PATIENT: At that time they did not seem to be effective at all.

DR. TALBOTT: That is one point that I think may be significant. What other medication did you take?

PATIENT: I took a penicillin preparation once a month for about five years.

DR. TALBOTT: That was probably a prophylactic preparation. It is important to note that this patient received penicillin for a long time without having any side effects and without any of the undesirable action associated with taking penicillin. This is especially important, because a diagnosis of disseminated or systemic lupus has been established recently in this patient. We wonder whether or not penicillin may aggravate the process or may have some inciting action in patients with lupus. However, there is no evidence that Mrs. B. is allergic or susceptible to any side effects of penicillin.

Mrs. B., would you tell us what new symptom appeared in addition to the joint disease about a year ago?

PATIENT: I began to have chest pains.

DR. TALBOTT: What was the diagnosis?

PATIENT: They thought it was pneumonia.

DR. TALBOTT: Did you have fluid in your chest?

PATIENT: Yes.

DR. TALBOTT: Did the doctor put a needle in to remove some fluid?

PATIENT: No.

DR. TALBOTT: Apparently, this was a pleural effusion, but not massive. The patient also had spotty pneumonitis. At that time, one of the interns on the service became especially interested in this problem of rheumatoid arthritis with systemic manifestations. Tell us what the intern thought this particular condition was, Mrs. B.

PATIENT: He believed that it was lupus.

DR. TALBOTT: That is indeed interesting. We value the work of our interns and assistant residents; they sometimes make a diagnosis for us. In this instance, it was probably the clinical acumen of the intern which led him to make this diagnosis.

In what way was this diagnosis proved?

PATIENT: A blood test was taken, and it proved to be positive.

DR. TALBOTT: Then you had positive lupus erythematosus cells in your peripheral blood in addition to what appeared to be typical rheumatoid arthritis. When we have an unusual complication of rheumatoid arthritis, one of the first things we consider, particularly in the female patient, is the possibility of systemic lupus.

I would like now to go back to 1947, when something happened to Mrs. B. which, in retrospect, appears to be probably a part of the same disease process. This finding supports the premise that systemic lupus is not a disease of a few months' or a year's duration, but a disease with a much longer clinical course. Would you tell us what happened to you in 1947, Mrs. B.?

PATIENT: Actually, the first attack occurred in 1945.

DR. TALBOTT: What kind of an attack was it, Mrs. B.?

PATIENT: An apparent epileptic seizure.

DR. TALBOTT: When was an electroencephalogram made?

PATIENT: I had no treatment of any kind after the first seizure in 1945. The next attack

was in 1947 and an electroencephalogram was done early in 1948.

DR. TALBOTT: Did the electroencephalogram indicate epilepsy?

PATIENT: No.

DR. TALBOTT: Nevertheless, the simplest anticonvulsive drug, phenobarbital, was prescribed. However, it was decided that Mrs. B. was not a suitable candidate for phenobarbital; subsequently, she was given DILANTIN®, and she has been taking it for the last five or six years.

In patients with lupus, we frequently obtain a past history of idiopathic epilepsy. It is possible that every patient with idiopathic epilepsy should be treated for lupus erythematosus, particularly if the condition is not associated with any familial history and if there is not a characteristic electroencephalographic pattern.

Mrs. B., what are you taking now for the lupus?

PATIENT: At the present time, I am taking 70 mg. of METICORTEN® daily.

DR. TALBOTT: On general principles, I do not recommend 70 mg. of Meticorten for anyone, no matter what the need for steroids might be. Most of my patients with unusual collagen diseases such as systemic lupus are taking 12, 15, 18 or 20 mg. of prednisone, Meticorten or prednisolone—not 60 or 70 mg. Is 70 mg. the highest dosage of Meticorten that you have taken?

PATIENT: At one time I was taking 100 mg. per day.

DR. TALBOTT: That is a huge dose, but apparently it was necessary to control the symptoms. What are you taking insofar as potassium replacement is concerned?

PATIENT: Nothing at present.

DR. TALBOTT: Then, with 70 mg. of Meticorten daily, you are no longer puffy as you were. You said you became bloated when you took cortisone several years ago.

PATIENT: That is right.

DR. TALBOTT: Although you have had a little swelling of your ankles, it hasn't been serious, at least in recent weeks or months?

PATIENT: The swelling was a blood clot which developed in my left leg.

DR. TALBOTT: That was a thrombophlebitis, which is another complication; but, insofar as your ability to tolerate 70 mg. of Meticorten a day is concerned, you are doing an excellent job. Will you tell us how you feel in comparison with how you have felt at various times in the past?

PATIENT: Actually, I feel about 1000 per cent better. Since I was released from my last hospital confinement, I have had much more interest in everything than I had had in the previous year, prior to the first diagnosis.

DR. TALBOTT: Even though you are not able to return to work, you are far from a sick person, Mrs. B. You are able to enjoy about 80 or 90 per cent of the things that you would if you were in normal health.

PATIENT: I am now able to do my own housework without assistance.

DR. TALBOTT: You told me you had had a kidney study.

PATIENT: Yes, I had the usual kidney tests.

DR. TALBOTT: In addition to the routine kidney function tests, you also had a trocar biopsy of the kidney. It is a relatively simple procedure. Drs. Kark and Pollak at the University of Illinois have done a great deal to put this procedure on a firm, stable basis. I believe that neither the kidney biopsy nor the routine urine tests revealed the characteristic wire-loop lesion that we frequently see in patients with lupus.

PATIENT: I think that is right.

DR. TALBOTT: Another interesting feature in relation to the diagnosis of bizarre situations is the positive serology we frequently see in patients with lupus. Although you are not aware that you have had a false positive serology, you did have at least one negative serology at the time of your marriage four years ago?

PATIENT: That is right.

DR. TALBOTT: So we presume that you are not one of those patients who have a false positive reaction.

Mrs. B. is far better now than she has been for a long time. She can tolerate and she benefits from large amounts of Meticorten. Certainly she will continue this medication for some time.

CRITICAL DISEASES—*Fourth of a Series*

The Nephrotic Syndrome in Adults

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MORTON H. MAXWELL

THE nephrotic syndrome is a disorder with only one constant clinical manifestation, namely, edema. It is diagnosed, however, in the laboratory by evidence of massive proteinuria, a low concentration of plasma albumin, and a high concentration of serum cholesterol. It may or may not be accompanied by high blood pressure and by evidence of reduced kidney function. The urinary sediment is characterized by oval fat bodies and fatty droplets, but also may contain red blood cells. The nephrotic syndrome may occur in the course of chronic glomerulonephritis, long-standing diabetes, amyloidosis, disseminated lupus erythematosus, secondary syphilis or bilateral thrombosis of the renal veins. It also may occur after the administration of certain drugs (TRIDIONE®, gold salts), or following bee stings or exposure to poison oak. Often, no cause or associated condition can be found.

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Incidence, Natural Course and Etiology

Because the nephrotic syndrome is most common in children below the age of five years, there is little statistical data available on its incidence, natural course, or response to therapy in adults. It is by no means, however, a rare disorder. On the medical service of the Veterans Administration Hospital in Los Angeles, we have seen an average of approximately 18 new cases per year for the past five years.

In the past, it has been assumed that almost

all instances of unexplained nephrotic syndrome seen in adults could be attributed to undiagnosed chronic glomerulonephritis. Preliminary renal biopsy studies, however, have shown that this may not be the case.[1] It would appear, instead, that probably not more than one-half of adults with the nephrotic syndrome have chronic glomerulonephritis; the majority of the remainder have diabetes, disseminated lupus erythematosus or amyloidosis, with rarer causes of the disorder accounting for a small percentage.

The natural course of the nephrotic syndrome in adults is unpredictable and varies with its cause. The majority of patients eventually die of renal failure. Although the outcome in children is more favorable than in adults, recent data suggest that there is no abrupt change in the mortality rate from childhood to adulthood, which supports the view that the nephrotic syndrome may represent the same disease in children and in adults.[2] In an untreated patient, edema of variable severity may wax and wane, and may be constant or intermittent. Intervals of from a few weeks to as long as five years of complete clinical remission without proteinuria may be followed by a recurrence. The edema may be accompanied by constitutional manifestations such as anorexia, fatigue, nausea and vomiting, diarrhea and irritability. The increased susceptibility to bacterial infection regularly seen in the childhood disorder is rare in adults. A prognosis is difficult on clinical grounds. Though persistent high blood pressure and uremia portend a gloomy outlook, complete healing occurs in some cases in which these findings are present. Recovery has been reported after active disease has lasted for 156 months, and patients with persistent proteinuria have been followed for 30 years after the onset.

More important than statistical data is the ability to make a prognosis in any individual case. Most helpful in this regard are: (1) serial tests of renal function (urea clearance, serum creatinine level) and (2) renal biopsy. If the urea clearance is markedly reduced or if the concentration of serum creatinine is elevated over a long period of time, it can be said that recovery cannot be expected. Individual prognosis may also be predicted on the extent and severity of glomerular involvement on renal biopsy. In cases in which there is extensive glomerular hyalinization, regardless of cause, the disease will generally run a downhill course. As more is learned about the distinguishing features of the various forms of the nephrotic syndrome, predictability will be improved. Lupus nephritis, for example, progresses more rapidly and inexorably than glomerulonephritis.[3] Nephrosis caused by diabetic nephropathy and amyloidosis may be resistant to all forms of therapy.[4]

It is, therefore, incumbent on the clinician to distinguish the different disease entities when possible. The presence of diabetes may be suspected when there is a positive family history of this disorder, in the presence of glycosuria or hyperglycemia, or when there is a typical retinopathy. Diabetic nephropathy is usually accompanied by moderate to marked hypertension.*All patients with the nephrotic syndrome should be carefully questioned and examined for evidence of disseminated lupus erythematosus. A history of fever, skin rashes, sensitivity to sunlight, serous effusions, Raynaud's phenomenon, or arthralgia is suggestive. The diagnosis may be confirmed in the laboratory when hyperglobulinemia, a telescoped urinary sediment, leukopenia, or L.E. cells are found.

Amyloidosis is most likely to be associated with chronic suppurative diseases, tuberculosis, rheumatoid arthritis or ulcerative colitis. A large liver or spleen may be palpable, and there may be a high concentration of gamma globulin in the serum as contrasted with the low concentration usually present in the nephrotic syndrome. A definitive diagnosis sometimes can be made by the Congo red test or gingival biopsy, but biopsy of the kidney or liver may be necessary. Bilateral obstruction of renal veins can only be suspected if extensive venous thromboses are present in other regions, if increased venous pressure or col-

*In the past year, we have made a positive diagnosis of diabetes mellitus in two patients with the nephrotic syndrome in whom glycosuria was not present and fasting blood sugar values were in the high range of normal as shown by glucose tolerance tests.

lateral circulation is observed, or if there is an underlying disorder likely to be associated with thrombosis of the inferior vena cava (hepatoma, Hodgkin's disease, etc.). Secondary syphilis is now rare as a cause of the nephrotic syndrome. Its diagnosis will depend on a history of primary syphilis and on serologic tests.

Etiology of the nephrotic syndrome—a unitarian concept—There has been disagreement for many years concerning the relationship between so-called pure lipoid nephrosis (seen mainly in children) and the nephrotic syndrome occurring as a phase of diffuse glomerulonephritis. Increasing evidence points to a unitarian concept embracing all varieties of the nephrotic syndrome, i.e., an antigen-antibody reaction which takes place in the glomeruli of susceptible persons and causes the clinical picture of the nephrotic syndrome.[5] The clinical pattern may vary depending on the type and strength of the initiating antigen and on largely unknown host factors, such as age, previous exposure to the same antigen, and hereditary patterns.

Favoring the unitarian hypothesis are the following: (1) In experimental nephritis in rats, small doses of antikidney serum produce diffuse glomerulonephritis, while larger doses of the same serum result in lipoid nephrosis;[6] (2) despite the failure of some investigators to identify glomerular abnormalities in lipoid nephrosis by light microscopy, recent studies with the electron microscope have revealed consistent changes;[7] and (3) Vernier, Brunson and Good[8] observed four children of a single family, each of whom had various types of nephrosis. One had transient "pure" nephrosis. A second died of renal failure and was found to have chronic glomerulonephritis. The third had chronic mixed nephrosis and nephritis, and renal biopsy showed subacute glomerulonephritis. The fourth had persistent "pure" nephrosis, and biopsy revealed a normal kidney. Electron microscopy[9] showed similar and characteristic changes in the glomeruli and basement membranes in all four cases. These changes were present regardless of the clinical phase of the disease or state of the pathologic process observed by light microscopy. Since these children belonged to a single family, it is presumed that the cause of the nephrosis was the same in all four cases.

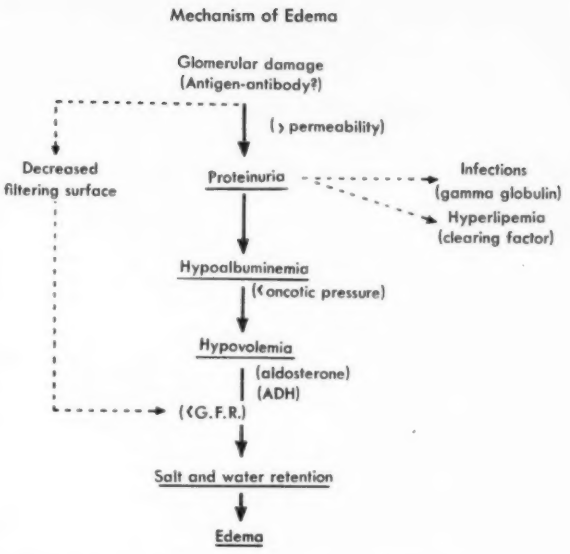

FIGURE 1. Mechanism of edema in the nephrotic syndrome. An antigen-antibody reaction localized in the glomerulus causes increased glomerular permeability and loss of large amounts of plasma proteins in the urine. The resultant hypoalbuminemia causes disequilibrium in the exchange of fluid at the capillary bed, with movement of fluid into the tissues and a decreased blood volume. The hypovolemia, probably by increased aldosterone secretion (and in extreme cases by increased antidiuretic hormone production), results in increased reabsorption of salt and water by the renal tubules. Thus edema is started by the low concentration of plasma albumin and increased and perpetuated by renal salt retention. The dotted arrows indicate: (1) that the initial glomerular damage may also decrease filtration rate and thus contribute to the edema, and (2) that the proteinuria probably also causes hyperlipemia and, by the loss of gamma globulin, increased susceptibility to infection.

Pathogenesis

Despite some minor points of disagreement, the various clinical, physiologic and anatomic studies all tend to support an essentially simple chain of events in the pathogenesis of the nephrotic syndrome (figure 1). The cornerstone of this concept is that the initial event is an anatomic alteration in the glomerular membrane which renders it more permeable to protein. The consequent loss of albumin in the

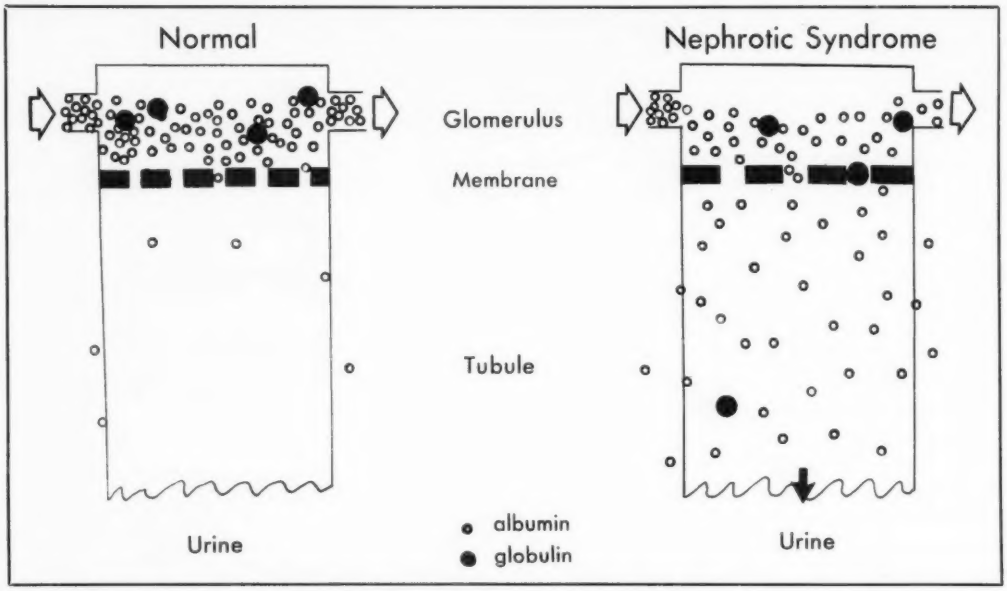

FIGURE 2. Mechanism of proteinuria in the nephrotic syndrome. In the normal glomerulus, on the left, the average "pore" size will permit the passage of only occasional small molecules of albumin. These are all absorbed by the renal tubular cells, so that there is no protein in the urine. The nephrotic glomerulus, on the right, contains a decreased number of "pores," but they are larger than normal. There is consequently a leakage of protein through the glomerular membrane, the smaller albumin molecules escaping more readily than the larger globulin molecules. Since the tubules have a limited capacity for protein reabsorption, massive proteinuria ensues.

urine leads directly or indirectly to all of the other observed alterations, namely, a low concentration of serum protein, an increased concentration of blood lipids, and edema.

Proteinuria—The normal glomerulus acts somewhat like a sieve with various-sized holes or pores.[10] In the nephrotic syndrome, damage to the glomerular membrane enlarges the size of these pores, so that the larger protein molecules, to which the glomerular membrane is ordinarily impermeable, are allowed to escape into the glomerular filtrate and thence to the urine, resulting in marked proteinuria (figure 2). The amount of each type of protein excreted in the urine varies roughly inversely with its molecular size. Albumin, the smallest protein molecule, therefore, accounts for well over 50 per cent of the protein in the urine. This concept of the sievelike role of the glomerulus in filtration is supported by electron microscopy of the normal kidney, in which either Hall's "pores in the lamina densa"[11] or Farquhar's "holes in the basement membrane"[9] appear to be the proper size to permit the filtration of only some of the albumin molecules.

Hypoalbuminemia—It is generally accepted that the decrease in the concentration of serum albumin in cases of the nephrotic syndrome results from the massive proteinuria. As would be anticipated from urinary excretion, the alpha$_1$ and gamma globulins are decreased in the serum, whereas, the larger alpha$_2$ globulins and the beta globulins are increased. The markedly decreased gamma globulin, which normally carries most natural antibodies, probably accounts in part for the increased susceptibility to infection.

Hyperlipemia—The concentrations of cholesterol and phospholipids in the serum are markedly elevated in cases of the nephrotic syndrome, and produce a milky serum. In a classic series of experiments on nephrotic rats, Rosenman, Byers and Friedman[12] established that the hyperlipemia is secondary to the plasma albumin deficiency. This is probably re-

lated to the transport role of albumin in the normal lipolysis of fatty acids.

Edema—Edema is frequently the only clinical manifestation of the nephrotic syndrome. The decreased concentration of plasma albumin is undoubtedly the initiating mechanism in the edema formation. In accordance with the Starling hypothesis, hypoalbuminemia results in a lowered plasma colloid osmotic pressure (figure 3), which permits the transfer of fluid from the circulation to the interstitial space. This is substantiated clinically, since the presence or absence of edema can generally be correlated with the concentration of serum albumin. If the concentration is below 1 gm. per 100 ml., edema is invariably present; while at concentrations between 1 and 2 gm. per 100 ml., edema can usually be controlled by low salt intake or by the use of diuretics.[13]

Although decreased colloid osmotic pressure may initiate the movement of fluid into the interstitial space, it cannot account for the accumulation or perpetuation of massive edema; for this, excessive retention of salt and water by the kidneys must be invoked. It would appear that the initial movement of fluid from the vascular to the interstitial compartment results in a decreased blood volume. This decreased blood volume, if marked, can result in a lowered glomerular filtration rate and/or increased secretion of antidiuretic hormone, both of which would result in fluid retention. Although a decreased glomerular filtration rate, which increases with diuresis, has been observed in some patients with the nephrotic syndrome, other patients have normal or supernormal kidney function. There is no good evidence supporting increased antidiuretic hormone activity in the nephrotic syndrome. Decreased glomerular filtration and excess antidiuretic hormone, therefore, can be only ancillary factors in the salt and water retention.

By exclusion, the edema must be the result of increased tubular reabsorption of salt and water. It has been shown that the urine of patients with the nephrotic syndrome, as in other edematous states, contains large amounts of the adrenal salt-retaining hormone, aldosterone.[14] The aldosterone content of the urine decreases with diuresis, whether spontaneous or induced. It is likely that the reduced blood volume, perhaps through "volume receptors" in the arterial side of the circulation,[15] stimu-

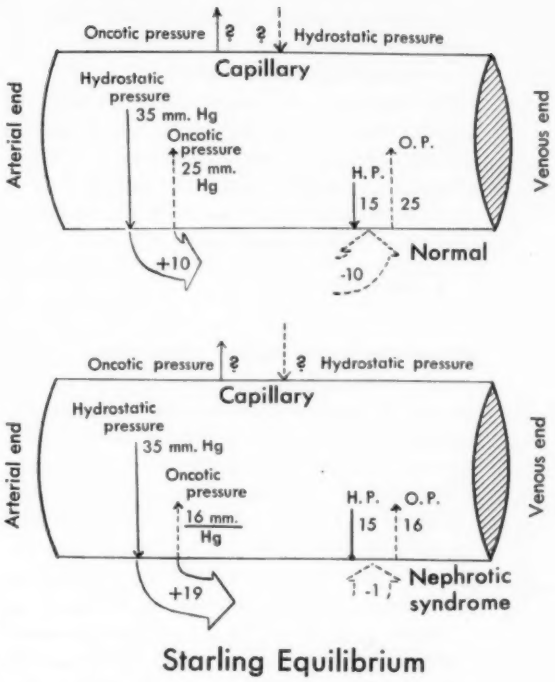

FIGURE 3. Starling equilibrium in normal capillary and in the nephrotic syndrome. Solid arrows indicate forces tending to cause movement of fluid from the vascular system into the tissues. Broken arrows indicate opposing forces. In the normal capillary (upper diagram), fluid exchange with the tissues is effected by a balance between hydrostatic pressure tending to force fluid out of the blood vessel and plasma oncotic pressure tending to hold fluid in. At the arterial end, the high hydrostatic pressure causes movement into the tissues. As blood passes through the capillary bed, the hydrostatic pressure diminishes, and at the venous end it is exceeded by the fixed oncotic pressure, thus permitting fluid to return into the vascular system. There is thus no net gain or loss of fluid from the blood. In the nephrotic syndrome (lower diagram), low concentrations of plasma albumin result in decreased oncotic pressure, upsetting the normal equilibrium and causing net movement of fluid from the blood into the tissues, initiating edema formation. The hydrostatic and oncotic pressures in the tissues generally play an insignificant role in fluid exchange. As indicated in the lower diagram, however, accumulation of edema may be partially limited by increased tissue (hydrostatic) pressure caused by the edema fluid itself.

lates the production of aldosterone which in turn causes renal retention of salt and water, and eventually clinical edema.

In summary, then, it can be said that the primary defect in the nephrotic syndrome is a glomerular lesion permitting the excessive loss of urinary proteins. The proteinuria in turn is directly or indirectly responsible for all of the other major phenomena of this disease.

Treatment

The management of adults with the nephrotic syndrome must be individualized and highly resourceful. Since the disorder is not so uniform in adults as it is in children, it is not possible to employ a precise plan of therapy in all cases. In a patient with quiescent disseminated lupus erythematosus, for example, it might be preferable to control minimal edema with moderate salt restriction and administration of diuretics rather than to risk an exacerbation of systemic symptoms following the termination of a course of steroid therapy; whereas, progressively larger doses of steroids will at times partially reverse the basic glomerular lesion in a patient with diffuse glomerulonephritis. If a renal biopsy shows that amyloidosis is responsible for the nephrotic syndrome in a patient with ulcerative colitis, colectomy may be the treatment of choice.

Some general principles of therapy, however, can be advocated, with individual variations depending on the clinical situation and on the ingenuity of the physician.

Diet—Moderate salt restriction is usually recommended, and, following spontaneous or induced diuresis in some patients, reaccumulation of edema can be prevented by salt restriction alone. An intake of between 2 and 4 gm. of sodium chloride will often accomplish this purpose without the risk of causing salt depletion. This amount of salt is contained in a diet which does not contain obviously salty foods (potato chips, pickles, anchovies, etc.). It allows the use of small amounts of salt in the cooking, but does not permit any additional salt at the table. Sometimes, it is necessary to limit the ingestion of salt more rigidly, which presents some risk of a "low salt syndrome." The presence of this syndrome may be suspected by a weight gain despite very low sodium intake, and by lethargy, hypotension and progressive azotemia. During the use of 800 mg. or less of sodium, serum and urine electrolytes should be checked periodically.

There is still considerable controversy on the proper amount of protein in the diet. There is no clinical evidence that prolonged low protein intake has any beneficial effect in the nephrotic syndrome. There is evidence, on the other hand, that the nephrotic syndrome is often accompanied by severe protein depletion and that a high protein diet promotes regeneration of the serum proteins and sometimes causes clinical improvement.[16] We, therefore, advocate a diet containing more than 100 gm. of protein and about 3000 calories, leaving the choice of protein up to the patient.* A high protein intake is interdicted in cases of advanced uremia with acidosis.

Activity—There is little indication for rest in bed except in the treatment of massive edema. If this condition is present, rest in bed may result in a modest diuresis or may potentiate diuretic agents. Strenuous physical exertion, of course, should be avoided. In several of our cases, prolonged rest in bed in the supine position aggravated anorexia, nausea and other gastrointestinal symptoms, which were subsequently relieved by keeping the patients in a seated position.[17] This suggests that these symptoms may have been caused by edema of the gastrointestinal tract.

Infections—Infections are more of a problem in children than in adults. In our experience, there has not been a higher incidence of bacterial infections among adults with the nephrotic syndrome than among the general hospital population.[17] We, therefore, do not use antibiotics prophylactically, even during the use of steroids.

Relief of edema—Use of diuretics—The various diuretics, either alone or in combination, are useful mainly in cases in which steroid therapy is contraindicated or has proved

*When it has been necessary to advocate a very low salt diet, we have found that unshelled peanuts in large quantity seem to be a palatable protein supplement. One pound of peanuts contains 130 gm. of protein and 210 gm. of fat.

ineffectual. In these instances, we try to potentiate the mercurial diuretics with ammonium chloride (12 gm. per day for three days preceding the mercurial injection), by rest in bed (for 24 hours after the injection), and by the administration of aminophylline (0.5 gm. intravenously 60 minutes after the injection). At times, the simultaneous administration of ammonium chloride and DIAMOX® followed by the administration of the mercurial diuretics has proved effective.

Mechanical removal of edema fluid—In the presence of tense ascites, paracentesis may be of benefit. Southey's tubes have also been effective. Before using Southey's tubes, it is important to keep the patient in a seated position with the feet dependent for at least 24 hours to permit the orthostatic accumulation of edema fluid in the lower extremities. We have employed peritoneal dialysis, by using a hyperosmotic solution (10 per cent solution of dextrose) in three cases, and we have successfully removed as much as 40 lb. of edema fluid.[18]

Plasma volume expanders—Concentrated human serum albumin given intravenously in a dose of 50 gm. per day for several days results in diuresis in about one-half of patients with the nephrotic syndrome, presumably because of its dual effect in raising the concentration of serum albumin and expanding plasma volume. The diuresis effected by albumin, as with diuretics, is usually short-lived unless the use of albumin is followed by rigorous salt restriction. In one patient who was resistant to mercurial diuretics, salt-poor albumin and steroids, when given individually, the concomitant use of concentrated albumin and steroids caused diuresis. Other plasma expanders, such as dextran, acacia and gelatin, are seldom used in these cases.

Miscellaneous measures—Nitrogen mustards induce diuresis in about one-third of the cases and may occasionally be indicated in cases in which the patients cannot tolerate or do not respond to the steroids. The details of therapy are as follows: A dose of 0.1 mg. per kilogram of actual body weight is given intravenously in a 5 per cent solution of dextrose in water on four successive days. Each injection is followed by infusion of 250 ml. of a 5 per cent solution of dextrose in water. Twenty-five milligrams of chlorpromazine hydrochloride is given intramuscularly before subsequent infusions if nausea occurred previously. As many as four courses may be given if the peripheral blood picture indicates recovery of the depressed bone marrow.

Steroid therapy—Treatment of the nephrotic syndrome with ACTH, cortisone or prednisone often induces a profuse diuresis similar to that which may occur spontaneously. In many instances, such diuresis is accompanied by an increased filtration rate, reduced glomerular permeability, decreased urinary excretion of protein and aldosterone, reduction in the concentration of serum cholesterol and an increase in the concentration of plasma albumin. Because steroids may thus completely reverse all the clinical and biochemical manifestations of the nephrotic syndrome, it is thought that they favorably influence the basic disease process, possibly by suppressing antibody formation.

If steroids are administered for a period of 10 days to two weeks and their administration then is stopped abruptly, diuresis will ensue in about two-thirds of the patients; another 10 per cent will respond after a second or third course of therapy. Without further treatment, a large number of relapses will occur within a year. Prolonged administration of steroids will prevent many of these relapses.[19] Although there is a paucity of data, it is believed that adults probably respond as well as children.[20] There is suggestive evidence that patients suffering from amyloidosis, diabetic nephropathy, or disseminated lupus erythematosus will be unresponsive to steroids, and that these diseases should be eliminated before intensive steroid therapy is attempted. In a statistical study of 780 children with the nephrotic syndrome, Riley and his associates[21] concluded that prolonged steroid therapy not only improved the clinical status, but also extended life. Recent data tend to support this conclusion in cases in which the patients are adults.

Our present plan of therapy is as follows: An initial course of prednisone, 15 mg. every six hours, is given for two weeks, and the ad-

ministration then is stopped abruptly.* If diuresis does not then occur within one week, another course of prednisone is given for 28 days. If diuresis has occurred during therapy, the patient is given a five day rest period, and then 15 mg. of prednisone is administered every six hours for three consecutive days of each week. If no diuresis has occurred, the rest period is extended to two weeks, and then the intermittent administration of prednisone is started in the same dosage used in the group that responded.† During steroid therapy, a diet containing 200 mg. of sodium is prescribed, and all patients are given 4 gm. of potassium chloride a day. Aluminum hydroxide gel and a bland diet serve to prevent the gastric complications of steroid therapy. No routine prophylactic antibiotics are given.

During the initial course of treatment, patients are kept in bed in the hospital. Body weight, urinary volume and blood pressure are observed daily, and the values for the serum electrolytes, creatinine, as well as the urinary proteins, are determined three times a week. The main indications for stopping therapy are a sudden and marked increase in blood pressure or a generalized infection. Other limiting complications, such as perforation of a peptic ulcer, are rare.

Intermittent therapy is adjusted on an outpatient basis at biweekly intervals. The patients record their own weight daily and report to the hospital immediately if there is any undue gain in weight. If there is a gain of more than 5 lb. or a definite increase in the excretion of protein, daily administration of prednisone is resumed until these abnormalities are reversed or for a maximal period of 28 days. The aim of therapy is to keep the patient free of edema and to completely eliminate (or at least markedly reduce) proteinuria. When the urine has been free of albumin for three months, prednisone is given for three consecutive days every other week for three months, every fourth week for three months, and it is then discontinued. If edema or increased proteinuria occurs, the schedule immediately reverts back to three days a week. When proteinuria does not diminish during intermittent therapy, the administration of steroids is discontinued after one year. Their administration is started again if protein excretion increases markedly.‡

Most of our patients show some of the features of hypercorticism (acne, moonface, glycosuria, mildly elevated blood pressure) even while on intermittent therapy. In only one patient did a generalized infection develop, and it was easily cured with antibiotics while the administration of steroids was continued. Osteoporosis and vertebral collapse have been reported to have occurred in cases in which the administration of steroids was continued for a long time, but we have not seen these complications. If mild hypertension is present, it can be treated with Rauwolfia drugs, but prolonged severe hypertension is a relative contraindication to steroid therapy. Azotemia is not a contraindication to therapy, and indeed improvement of azotemia may occur during the administration of steroids.

It must always be remembered that the nephrotic syndrome is generally a chronic and discouraging disorder for the patient. Flexibility rather than rigidity is the rule. Brief lapses from sodium restriction should be allowed on special occasions, such as holidays and birthdays. At times, great ingenuity is required in devising a diet which will ensure adequate nutrition and still prove palatable. With a mixed nephrotic syndrome and terminal uremia, it is often kinder to permit the patient to spend his last remaining days at home and to partially control his edema with salt restriction or diuretics, rather than to hospitalize him for steroid therapy. He should be encouraged and made to feel that by keeping

*There seems to be little difference in response with the various steroids. Cortisone, 100 mg. every six hours; hydrocortisone, 80 mg. every six hours; or ACTH gel, 40 units intramuscularly every 12 hours, may be substituted for prednisone.

†Diuresis has occurred in three patients in whom the intermittent administration of prednisone was started immediately. This plan of therapy now is being tried in alternate cases.

‡Riley and his associates[21] have reported that the sedimentation rate of the erythrocytes is just as useful as quantitative determination of the protein as a guide to the results of treatment. If this proves to be true, it will simplify the follow-up care of patients.

careful weight records or by testing his urine for protein he is an essential part of the therapeutic team. Adverse effects of treatment such as acne should be explained in advance. With an honest but truly optimistic attitude on the part of the physician, the handling of these patients is usually gratifying.

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New Award for Medical Writing

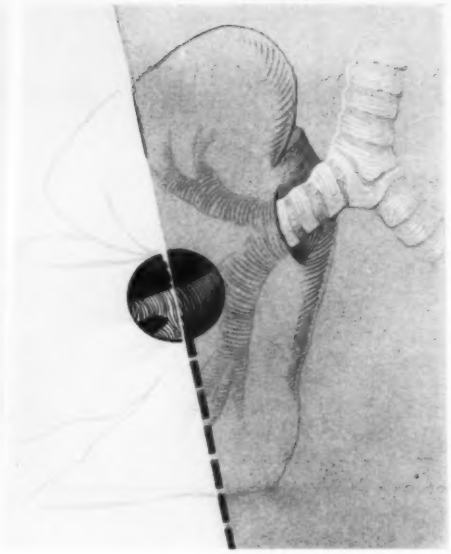
An award for the best unpublished manuscript for a short book on a clinical subject in the field of internal medicine has been announced by the editors of "Modern Medical Monographs." Purpose of the award is to stimulate physicians to achieve high standards of medical writing in the classic monograph form. The winner will receive $500 and, if judged suitable, the monograph will be published. A committee of the American Medical Writers' Association will screen entries for style and clarity. Information as to contest rules and manuscript requirements is available from Modern Medical Monographs, 381 Fourth Avenue, New York 16.

SCIENTIFIC EXHIBIT

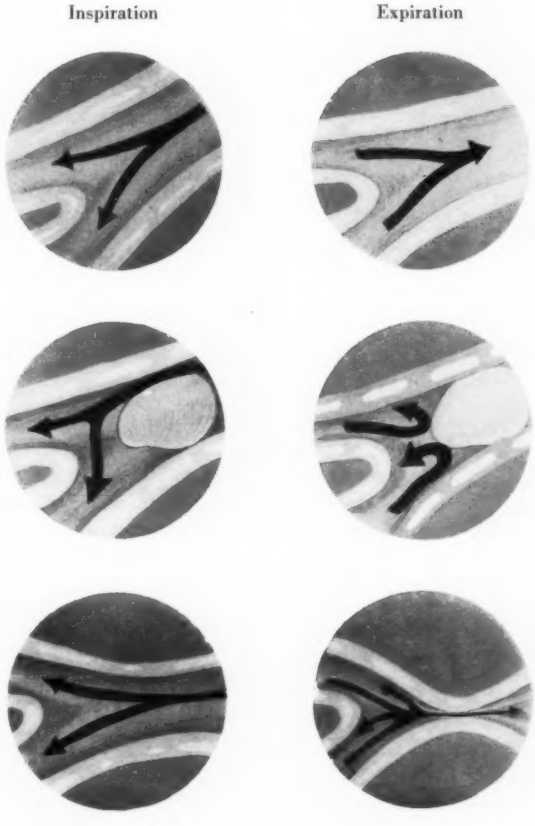
Lobar Emphysema in the Young

EUGENE F. VAN EPPS AND HARRY W. FISCHER
State University of Iowa College of Medicine, Iowa City

EMPHYSEMA of a lobe of the lung in an infant or a young child is being recognized as a cause of severe respiratory difficulty which if untreated often leads to death. Pathogenesis is not always clear but many cases are due to abnormality of lobar bronchial cartilage. The abnormal bronchus allows air to enter the lobe more easily than it can be removed. Progressive overexpansion leads to poor respiratory exchange within the lobe itself and compression of adjacent normal lung. Lobectomy is curative. Nonsurgical measures may result in damage from anoxia or death. Although this condition is not frequent in occurrence, all physicians, and radiologists, pediatricians and thoracic surgeons in particular, should become acquainted with the syndrome. More awareness may lead to more frequent diagnosis and to understanding of the problem.



Lobar emphysema is considered an obstructive emphysema of a single lobe, occurring in an infant or a young child with severe respiratory distress. Probably of congenital origin, its incidence is unrelated to infection or other event. Anoxia and death can ensue rapidly if the condition is unrecognized and untreated.



NORMAL

The bronchus widens and lengthens on inspiration, shortens and narrows on expiration.

CHECK VALVE FROM FOREIGN BODY

Air enters on inspiration when the bronchus is widened, but on expiration it is trapped when a foreign body obstructs narrowed bronchus.

LOBAR EMPHYSEMA

A similar check valve situation is thought to exist in an upper or middle lobe bronchus. Air enters the lobe on inspiration but is expelled with difficulty. Increased bronchial collapsibility from absence or malacia of cartilage, or other factors not clearly understood, may be responsible.

In addition to poor respiratory exchange in the involved lobe, lung function is embarrassed by pressure of the huge lobe. Anoxia, dyspnea and cyanosis result.

DO YOU THINK OF

Lobar Emphysema

WHEN YOU SEE A CHILD IN RESPIRATORY DISTRESS?

To Diagnose

History and Physical Examination

Not related to infection or prematurity
Signs of respiratory distress
  Dyspnea and accessory findings
  Cyanosis
Differences in ventilation between the hemithoraces
Shift in mediastinal structures
Absence of other lesions such as congenital heart disease, intracranial damage

SINCE PHYSICAL EXAMINATION OFTEN MAY BE CONFUSING, HAVE NO HESITATION IN OBTAINING CHEST FILMS!

Radiology

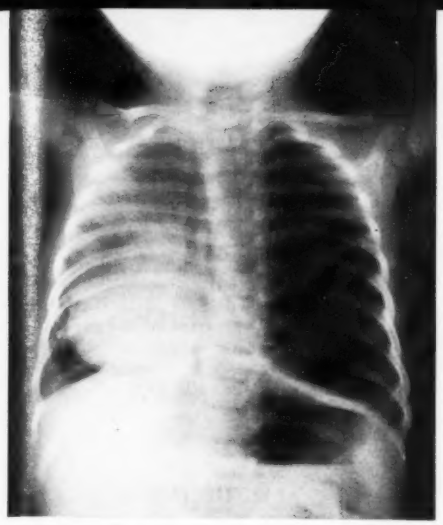
Large area of pronounced radiolucency which retains lung markings
Depressed diaphragm on radiolucent side
Shift of mediastinum away from radiolucent side
Compression atelectasis of other lung tissue
Collapse of right lower lobe in right middle lobar emphysema is typical
Increased radiolucency, anterior mediastinum
Increased anteroposterior diameter of chest
Inspiration-expiration films and fluoroscopy
  Accentuation of the above findings in expiration
  Diaphragm of radiolucent side is less mobile

The above points should allow a differentiation from atelectasis with compensatory emphysema, foreign body aspiration, pneumatoceles, pneumothorax, cystic lung disease, giant solitary cyst, lung abscess, diaphragmatic hernia, tracheoesophageal fistula.

Bronchoscopy

Excludes other lesions, particularly atelectasis with compensatory emphysema.

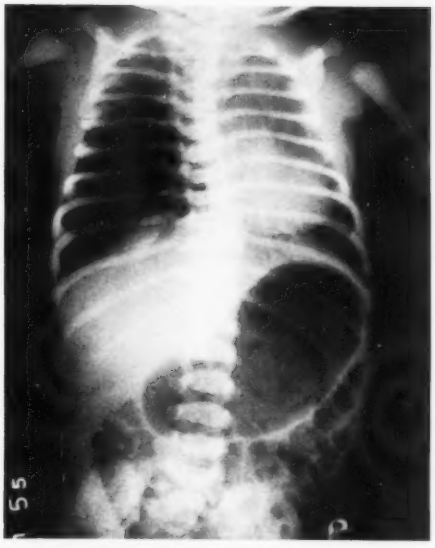
Occasionally may show abnormal collapsibility of a lobar bronchus.



Left upper lobar emphysema

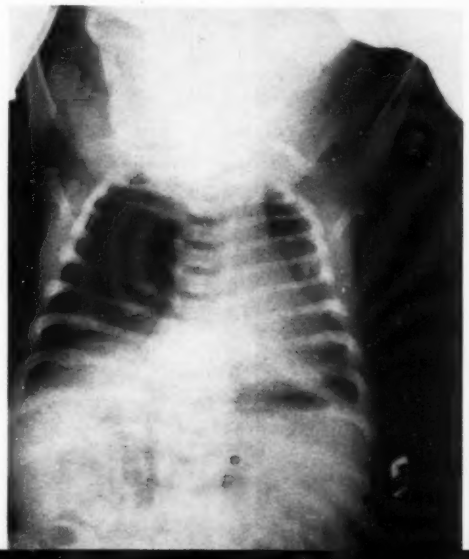
Lateral view

Lateral view



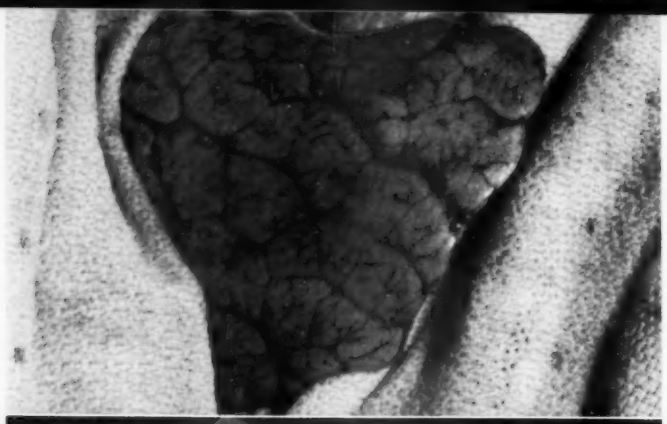
Right middle lobar emphysema

Postoperative



Right upper lobar emphysema

Postoperative



Treatment

SURGERY

Almost all cases of lobar emphysema will need surgical treatment for alleviation of the condition, frequently on an emergency basis. Lobectomy is curative. Postoperatively the child does well.

ANESTHESIA

Although lobectomy has a low mortality rate, there is added danger during the anesthetic induction. Physiologic disturbances are accentuated at this time, placing the child in an even more precarious position until the chest is opened and the pressure from the emphysematous lobe is relieved.

CONSERVATIVE TREATMENT

Oxygen, tracheobronchial aspiration and humidification of air are appropriate initially and until a diagnosis is made. In a few cases conservative measures alone may be sufficient to allow the child to return to a normal respiratory state.

BRONCHOSCOPY

Bronchoscopy is of value in clearing mucus from the lower part of the respiratory tract and in differentiating lobar emphysema from other entities, particularly atelectasis with compensatory emphysema.

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FUNCTION OF VITAL ORGANS—*Second of a Series*

Hepatic Function

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HANS POPPER

As every physician knows, the liver has a great variety of functions and therefore the number of possible tests of hepatic function is virtually unlimited. Actually such tests were among the first described when the principle of functional diagnosis was introduced into clinical medicine more than half a century ago. Nevertheless today the role of hepatic function in diagnosis and treatment still is more argued and confusing than the functional diagnosis of virtually any other organ.

One can list several reasons for this state of affairs. Essential functions of the liver such as formation of blood glucose or protein and even detoxication do not lend themselves well to evaluation in clinical laboratory tests. Such functions are carried out in a context of a large number of interwoven metabolic processes. It is difficult, therefore, to establish a clear base line that is not influenced by alteration of functions of other organs. Moreover, the technics for determination of some of the specific products of the liver are still too difficult to be applied in the routine laboratory. There is expectation that with advances in chemistry and with ingenuity on the part of researchers usable technics will be worked out and proper conditions stabilized. This hope explains the flurry of hepatic function tests being presented to the practicing clinician through the years.

Both the basic scientist and the clinician, however, are becoming painfully aware that in most clinical problems it is not the alteration of hepatic function, particularly that of the specific hepatic cells, in which the clinician is interested. The liver, being in the center of the metabolism, is readily disturbed in the presence of more or less severe alterations in other organs. Tests of hepatic function, therefore, give abnormal results in a great variety of disease processes in which the involvement of the liver is of little or no clinical

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interest. Liver biopsy reveals a nonspecific reactive hepatitis in many diseases. Their differentiation from primary hepatic disease is of crucial clinical importance. Therefore, demonstration of disturbed hepatic function is not necessarily of advantage clinically. This is especially true for the differential diagnosis of jaundice. Some impairment of hepatocellular function is seen in every more severe type of jaundice, and its demonstration by hepatic function tests does not necessarily prove that the jaundice results from hepatocellular dysfunction. Thus, degree rather than presence of hepatocellular derangement is of diagnostic interest.

The difficulties presented characterize the function tests of the liver in contrast to those of other organs such as kidney, lung and pancreas; in the latter, demonstration of reduction of a basic function of the organ is of major clinical significance. These difficulties account for the aura of myth that clouds the hepatic function tests and explain why many clinicians discard them. They are by no means useless in clinical practice; it is rather necessary to use the tests for specific situations. The goal in the further development of functional diagnosis of the liver, therefore, is less the advancement of physiology of the liver than it is the coordinated use of the available information in a system, sometimes called profile, devised for a specific problem.

Examples of these specific problems, probably in order of importance, are the differentiation between surgical jaundice caused by tumors, calculi or strictures and the medical variety resulting from hepatitis and cirrhosis; differential diagnosis of hepatomegaly primarily to recognize cirrhosis; establishment of hepatic damage particularly to recognize toxic effects from medication or industrial exposure; prognosis in a patient with a known diagnosis, e.g., in preoperative management or in the course of viral hepatitis; recognition of alarm signs for imminent breakdown of hepatic function; differential diagnosis of neonatal jaundice; recognition of hepatic metastases and other space-occupying lesions; separation of chronic hepatitis from cirrhosis; and management of convalescence of viral hepatitis, to establish the presence of permanent damage that requires extended rest. For each situation listed, several of the hepatic tests may be useful. However, in the interest of laboratory economy as well as clinical simplicity it is desirable to restrict the number of hepatic tests as much as possible. I shall list several tests which enjoy great popularity at present, at least in this country, and give examples of the problems to which they apply. Any such selection is, of necessity, subjective.

Serum Alkaline Phosphatase

Phosphatases are enzymes which split inorganic phosphate from organic phosphorus compounds. They are essential in many metabolic processes in all cells of the body. The serum phosphatases with the peak of their activity on the alkaline side are derived to a great extent from the osteoblasts. Therefore, their activity is increased in bone diseases with significant osteoblastic activity, such as Paget's disease and metastatic carcinoma. They are also formed in the intestinal mucosa and possibly in the liver. For reasons still in dispute, the serum activity of alkaline phosphatases rises in hepatobiliary diseases, slightly in those accompanied by hepatocellular degeneration such as hepatitis and very conspicuously in those associated with bile stasis of either intrahepatic or extrahepatic cause.

This very significant laboratory indication of cholestasis makes the determination of serum alkaline phosphatase valuable in the differential diagnosis of jaundice in that it is in principle slightly elevated in the medical variety and conspicuously so in the surgical variety. However, in intrahepatic cholestasis, which may complicate any primary hepatic disease, the elevation of serum activity is equal to that in extrahepatic biliary obstruction. This raises a problem in the pure intrahepatic cholestasis which is as a rule designated as cholangiolitis. This condition is at present frequently seen as a result of administration of various drugs, particularly chlorpromazine and methyltestosterone.

In the absence of jaundice or when slight jaundice is present, the activity of serum alkaline phosphatase is elevated in disturbances of

the bile flow as in cholangitis or as a result of a residual stone in the extrahepatic or intrahepatic bile ducts after biliary surgery. It is also elevated, even in the absence of jaundice, in the presence of metastatic carcinoma and other space-occupying lesions such as abscesses, in granulomatous diseases such as hepatic tuberculosis and sarcoidosis, and also in cirrhosis or primary hepatic carcinoma.

Serum Protein Reactions

The liver has a profound influence on serum proteins. Apparently serum albumin and alpha globulins are formed by the hepatic cells. The largest serum proteins, the gamma globulins, are formed by the reticuloendothelial system, possibly including the hepatic Kupffer cells, whereas the origin of the beta globulins is doubtful. When the hepatic cells are damaged, albumin and some alpha globulins decrease while the gamma globulins as a rule increase, presumably because of stimulation of the Kupffer cells or other parts of the reticuloendothelial system by the hepatocellular damage. In cholestasis the beta globulins rise, while the gamma globulins usually do not rise conspicuously even in the presence of severe liver cell damage. An exception is superimposed bacterial infection which stimulates the reticuloendothelial system. The electrophoretic serum fractionation may thus mirror the hepatic alterations. However, long before the described principles were elucidated, simple protein reactions were developed on an empirical basis; only in recent years has some knowledge of the basic principles involved been gained.

In general, reduction of albumin and alpha globulin as well as elevation of gamma globulin reduce the stability of the serum proteins, thus creating a positive turbidity or flocculation reaction. This is characteristic of hepatocellular damage without severe cholestasis. Thus, independent of the degree of damage of the liver cells, in the medical type of jaundice the serum protein reactions tend to be positive; in the surgical type they are negative except when the condition is complicated by severe bacterial infection as in cholangitis. The flocculation tests, therefore, have great value in the differential diagnosis of jaundice regardless of the presence of hepatocellular damage. However, just as is the case with the alkaline phosphatase, differentiation is not made between intrahepatic and extrahepatic biliary obstruction.

Among the many variations of the serum protein reactions, probably the most popular is the cephalin flocculation of Hanger. This reaction becomes positive primarily because of reduction in alpha lipoproteins. Its abnormality is a good index of damage of the liver cells even in the absence of jaundice, and it is therefore a valuable screening procedure. However, results frequently are abnormal in nonspecific hepatic disorders such as various gastrointestinal or infectious diseases.

The thymol turbidity test of Maclagan is even more dependent on lipoproteins, but of the beta variety, and is more strongly influenced by elevation of serum gamma globulin than is cephalin flocculation. This test apparently is rather specific for viral hepatitis. Thymol turbidity is distinctly elevated in cases of viral hepatitis in which the other tests may show little abnormality, and therefore the test is useful as a screening procedure. While thymol turbidity as a rule is low in nutritional cirrhosis, it is high in the postnecrotic or posthepatitic type, sometimes without simultaneous elevation of the cephalin flocculation. This results mainly from the gamma globulin elevation, and the latter can be ascertained more specifically with other turbidity reactions—either the zinc sulfate turbidity of Kunkel or the ammonium sulfate turbidity of Huerga and Popper. Serum gamma globulin is particularly elevated in postnecrotic cirrhosis but it is also elevated in many chronic diseases, especially tuberculosis and sarcoidosis, and in most instances of multiple myeloma. Normal gamma globulin turbidity in the presence of jaundice is a valuable laboratory sign of cholestasis and therefore of surgical jaundice if intrahepatic cholestasis (cholangiolitis) can be excluded.

Since the serum protein reactions are technically very simple, it is advisable to perform at least two of them. The selection from the large number reported obviously depends on the experience of the laboratory.

Bile Pigment Studies

Determination of bile pigments in serum and urine as a diagnostic procedure has a long history. Only very recently has some clarity been obtained from the observation that the bilirubin formed by the reticuloendothelial system and circulating in the blood, previously called indirect reaction bilirubin, is a free compound, whereas the one that has passed through the liver cells, previously called direct-reacting or prompt-reacting form, is a bilirubin conjugated with glucuronides in a reaction similar to a detoxication. Some conjugation also occurs in the kidney. The glucuronides, being far more soluble, not only give the van den Bergh reaction immediately but also pass readily into the urine.

In jaundice associated with hepatocellular damage or cholestasis, the bilirubinemia is caused at least partly by glucuronides. The van den Bergh reaction is direct in both instances, and therefore does not differentiate between the two conditions. Consequently the bilirubin partition is useless in adult jaundiced patients with more than 6 mg. bilirubin in 100 ml. serum. Only in jaundice without impairment of bile flow, as in the hemolytic or retention type, neither of which, if pure, ever causes levels higher than 6 mg. per 100 ml. outside the neonatal period, does free bilirubin predominate. When these conditions are suspected, serum bilirubin partition is indicated. In general, therefore, the serum bilirubin level is of less value as a diagnostic sign than as an indication of the severity of the disease. Urinary bilirubin is as a rule higher in relation to the degree of jaundice in early stages of jaundice, and its determination may thus serve as a screening procedure.

Bilirubin is transformed in the intestine into a group of pigments designated as urobilinogen, some of which is absorbed into the blood stream and re-excreted by the liver. When liver cells are damaged, reabsorption is impaired and much urobilinogen appears in the urine. The same is supposedly true for hemolysis, when more bilirubin than normal enters the intestine. In contrast, in complete biliary obstruction, when no bilirubin enters the intestine, urobilinogen disappears from the urine. Simple qualitative tests for urinary bilirubin and urobilinogen are thus used effectively in the management of jaundice.

Cholesterol Partition

While all cells form cholesterol, serum cholesterol is mainly the product of the liver and therefore is reduced in severe hepatic injury. In contrast, in extrahepatic and intrahepatic biliary stasis, it rises markedly because of faulty excretion in the bile, as previously assumed, and also probably because of altered solubility in the presence of obstruction. Sometimes, particularly in the intrahepatic variety of biliary stasis, the serum cholesterol may rise to levels that result in its deposition in the skin as xanthomas. The liver, possibly under the influence of other organs, esterizes the cholesterol with fatty acids so that normally only one-third of the serum cholesterol is a free alcohol. In liver damage this esterification is faulty and the ratio of cholesterol esters to cholesterol drops. This occurs early in surgical jaundice because of the high total cholesterol level. In conditions such as these a drop of the cholesterol ratio is a sensitive but less ominous sign than it is in the presence of hepatitis.

Dye Excretion

The liver excretes many exogenous dyes through the bile. Different dyes have been measured in the blood, in the bile, in the urine, or by radioisotopic methods over the liver, the latter with a scintillation counter. The method most widely used is the clearance from the peripheral blood of BROMSULPHALEIN® administered intravenously. Abnormal retention of Bromsulphalein indicates impaired hepatic circulation, reduced ability of the liver cells to take up the dye, or its faulty excretion into the bile. The Bromsulphalein test is therefore of little value in differential diagnosis of jaundice. However, in the absence of jaundice it is among the most valuable tests to establish hepatitis or cirrhosis. The amount of the dye retained is also elevated in hepatic metastases, and, since clearance depends on hepatic circulation more than any other hepatic function

dies, abnormal retention occurs also in congestion of the liver or even in fever.

Other Tests

The list of tests just discussed, which includes determination of serum alkaline phosphatase, serum protein reactions (particularly cephalin flocculation, thymol turbidity and gamma globulin turbidity), urinary bilirubin and urobilinogen, cholesterol and cholesterol esters, and finally Bromsulphalein retention, can be extended. For instance, the prothrombin time is frequently prolonged in jaundice because of faulty absorption of vitamin K in the absence of bile acids from the intestine. On parenteral administration of vitamin K-like preparations, the prothrombin time becomes normal if the liver cells are not too damaged to produce sufficient serum proteins active in blood coagulation. However, rather elaborate technics are required in order to use this principle in the clinical evaluation of hepatic function. The simpler tests for prothrombin suffice to establish bleeding tendencies in liver diseases. Recently the serum level of glutamic oxalacetic and glutamic pyruvic transaminase has been introduced as a measure of necrosis of liver cells. This determination is acquiring increasing popularity especially because of the very high levels in the earlier stages of hepatocellular injury, e.g., in viral hepatitis. Finally, ammonia is being determined in fasting arterial blood as an index of hepatic coma, since ammonia is held responsible for the disturbance of the brain metabolism characteristic of this condition. However, elevated blood ammonia frequently reflects the cerebral disturbance which is the result of bypass of blood from the liver and therefore does not necessarily parallel hepatic coma as a sign of derangement of the liver itself.

Conclusion

The problem in the functional diagnosis of liver disease is establishment of altered structure rather than of disturbed function. Differential diagnosis between medical and surgical jaundice by laboratory means is difficult because intrahepatic cholestasis as a medical lesion gives the findings usually encountered in extrahepatic biliary obstruction, whereas an obstruction with superimposed bacterial infection presents the laboratory findings of a medical type of jaundice. Moreover, the nonspecific reactive hepatitis in any type of disease may provide the same findings as a primary liver disease. Full acquaintance and experience with a small number of tests are thus more valuable than the performance of an extensive profile. The results of the tests should be taken less on their own value than one would take the results of function tests of other organs. They rather deserve integration and correlation with the history, clinical findings and, if possible, observations at liver biopsy.

CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Case Report and Discussion

DR. ROBERT M. POSKE (internal medicine): A 35 year old white man, a machinist, entered Hines Veterans Administration Hospital in May 1957 complaining chiefly of pain in the left side of the chest and dyspnea of two months' duration.

The patient stated that he had not had diphtheria, scarlet fever, rheumatic fever or arthritis. He had had hay fever and asthma as a child, and also as late as 24 years of age. (This may be important, since the nephrotic syndrome developed subsequently; one of the major etiologic factors in this condition is an allergic diathesis in the family or the patient.)

In February 1944, when he was 22 years old, he had thrombophlebitis of the left leg. Varicose veins were present and may have contributed to the thrombotic episode. Two years later, while being separated from the Army, he was found to have a labile hypertension. Systolic pressure was 180 mm. Hg, and it fell to 120 after two or three hours of rest.

For 10 years he had had left frontal headaches, usually lasting three days. Occasionally he saw yellow and black spots before his eyes. He had experienced migratory paresthesias of the fingers, arms and legs for a year and a half and had lost 50 lb. during that time.

(Up to this point we are confronted with multiple and apparently unrelated symptoms which, if taken separately, might point toward some sort of anxiety reaction. Later, when the protocol suggests the possibility of a collagen disease, one wonders if some of these earlier complaints might be related to the oncoming disease. We know that in disseminated lupus erythematosus, for example, such things as a biologic false positive serologic test for syphilis, thrombophlebitis, paresthesias and headaches may precede the diagnosis of the disseminated disease by months or even years.)

During the year prior to admission to the hospital he had a variety of symptoms, including six episodes of bloody, crusty material produced from the nose and throat, intermittent periods of fever of 102 to 103° F. at two to

three week intervals, marked nausea, severe anorexia, occasional vomiting, dull left-sided backache with urinary frequency and nocturia, and intermittent anasarca. At one time, when he was very edematous, he weighed 208 lb. His "best weight" was 165 lb.

In March 1957, two months before admission, he had pain in the left side of the chest, dyspnea, a dull aching sensation in the left upper abdominal quadrant, and a "swishing" when he walked. Sleeping in a sitting position partially relieved the abdominal ache. (These symptoms suggest the presence of fluid and possibly air in the chest, abdomen or pericardium.) A private physician made numerous x-ray studies of the chest and upper gastrointestinal tract, and these reportedly were negative. The patient was referred to a hematologist, who made a diagnosis of infectious mononucleosis. (One wonders how the hematologist arrived at that diagnosis. Were abnormal lymphocytes seen on the blood smear? Was the spleen or liver palpable, or were heterophil agglutination tests positive? Since a collagen disease has been considered as a possibility in this case, it might be in order to mention that two patients in Harvey's series of cases of lupus had atypical lymphocytes in the peripheral blood—8 per cent and 9 per cent, respectively.)

After the diagnosis of infectious mononucleosis was made, the patient was placed on cortisone therapy. He received one to two tablets daily for 21 days. During that period he began to run a febrile course, with a temperature as high as 102° F. He also experienced chills, increasing weakness, fatigue and weight loss. He was hospitalized elsewhere for a diagnostic work-up, and during this three week period he had pneumonia and a kidney infection. He was also told that he was anemic. He was given 40 units of zinc corticotropin twice a week and 12 tablets of prednisone daily. Gradually the prednisone dosage was decreased to half a tablet twice daily. (His physician apparently believed in intermittent stimulation of the adrenal cortex with ACTH when corticosteroids are employed. We have not used ACTH in such situations at Hines, since we feel that laboratory or clinical evidence that it is of value is lacking. In fact, ACTH could be detrimental when employed in such a manner, since it might further suppress an anterior pituitary that is already inhibited by the corticosteroids.)

At various times the patient received antibiotics, mercurial diuretics, ammonium chloride and acetazolamide. During the two months before he was admitted to Hines, he noted severe dyspnea and marked anorexia. He also complained of cramping abdominal pains and a cough productive of blood-tinged sputum on occasion. The pain in the left side of the chest continued, and the anasarca fluctuated with the use of diuretics.

When admitted to Hines Veterans Administration Hospital, the patient appeared well nourished but chronically ill. He had a high fever and was having a chill at the time of examination. He was pale and had dependent and periorbital edema. Blood pressure was normal. His hair was coarse and brittle (probably due to the low metabolism of the nephrotic state, but it could also be the result of suppression of thyroid activity by corticosteroids; it is not known whether such an effect is the consequence of changes in the function of the thyroid gland itself or is due to secondary alterations of secretion or metabolism of thyroid-stimulating hormone). The fundi were normal. Shotty lymph nodes were felt in the axillae. Tenderness was elicited in the left wall of the chest over the region of the seventh rib anteriorly. The chest had an emphysematous configuration, and hyperresonance was noted on percussion. The second aortic heart sound was greater than the second pulmonic sound. A short grade 2 systolic murmur was heard. The liver and spleen were not palpable. Some tenderness in the left costovertebral angle was elicited by percussion and deep palpation. Knee jerk reflexes were absent, but Achilles tendon reflexes were present. (My neurologic friends tell me that selective loss of the knee jerk reflexes could be the result of atrophy of proximal or thigh muscle groups such as has been seen in dermatomyositis. I do not think that edema per se would prevent the eliciting of the knee jerk reflexes and not of the Achilles tendon reflexes.)

The laboratory studies revealed moderately severe anemia with a color index of approximately 1. Leukocyte count was slightly elevated, and progressive polymorphonuclear leukocytosis was noted. Eosinophilia was not present. Platelet count was 91,260. The protocol does not mention lupus preparations. Urinalyses disclosed 4 plus albumin, 10 to 15 white blood cells, numerous red blood cells and "occasional casts" but no sugar.

(A more detailed description of the casts would be helpful. Were these the red cell casts of acute glomerulonephritis, the hyaline and vacuolated cellular casts of the nephrotic syndrome, or the broad or renal-failure casts of chronic glomerulonephritis? At this point we might consider the concept of Krupp and associates of the "telescoped" urinary sediment. This term means the association in a single urinary sediment of the findings characteristic of acute glomerulonephritis, the nephrotic syndrome, and chronic glomerulonephritis. Krupp considered this situation "pathognomonic of visceral angiitis," but others have disagreed. In the case under discussion, urinalysis showed the red cells of acute glomerulonephritis and considerable albumin, which is seen in the nephrotic syndrome. Thus we might say that the urinary sediment was partially or incompletely "telescoped.")

A serologic test for syphilis was negative. Total protein was low, 4.8 gm., and the albumin-globulin ratio was 2.1 to 2.7. Cholesterol was elevated to 370 mg. A BROMSULPHALEIN® test showed 28 per cent retention of dye. (This test reflects the flow of blood through the liver, and abnormal results may be found in such conditions as congestive heart-failure and constrictive pericarditis as well as hepatocellular damage and biliary obstruction. The elevation in this case might be due to congestive heart-failure.)

Cephalin-cholesterol flocculation, thymol turbidity and other tests of liver function gave normal results. A two hour Watson test for urinary urobilinogen gave results within normal limits. Progressive retention of nitrogen was evident, the nonprotein nitrogen level rising from 123 to 264 mg. Carbon dioxide-combining powers of 7.4 to 14.4 mEq. indicated renal acidosis. Serum potassium varied from 5.1 to 5.7 mEq., and sodium from 128 to 142 mEq. Renal function tests gave abnormal results. The phenolsulfonphthalein test showed 10 per cent excretion in 40 minutes, and the urea clearance test was 8 per cent.

An electrocardiogram was interpreted as showing the changes of anterior myocardial ischemia. Blood cultures were negative. Hemolytic *Staphylococcus albus*, coagulase-negative, was cultured from the urine (I am inclined to think this was a contaminant organism because of its lack of pigment and its coagulase properties). *Escherichia coli* and *Streptococcus faecalis* were cultured from the mouth, where they are not ordinarily found (this might suggest the presence of a gastrocolic fistula, but more likely was the result of intensive antibiotic therapy).

An x-ray of the chest revealed an increase of the transverse cardiac diameter of 17 per cent above the predicted normal value. There was some blunting of the right costophrenic sinus, and in the right lower lung field an area was noted that was considered to be an old pleural reaction. The lungs were otherwise found to be clear.

The patient was given blood transfusions, two courses of nitrogen mustard, and several antibiotics—penicillin, 15,000,000 units intravenously daily, and streptomycin, tetracycline and chloramphenicol. He received 40 to 200 mg. of prednisone daily, and terminally 200 mg. of hydrocortisone intravenously daily. Recurrent monilial infections in the mouth became troublesome. Finally, pulmonary edema developed and the patient died after one month in the hospital.

Differential Diagnosis

The most striking feature of this case is the classic picture of the nephrotic syndrome, characterized by intermittent anasarca, proteinuria, hypoproteinemia with a low albumin fraction, and hypercholesteremia. Elevation of the blood cholesterol would speak against the pseudonephrotic state; however, the short and stormy terminal illness would be compatible with that "variant." The nephrotic syndrome may be seen in association with such diseases

as secondary syphilis, toxemia of pregnancy, amyloidosis, intercapillary glomerulosclerosis (Kimmelstiel-Wilson syndrome), bilateral obstruction of the renal veins, membranous glomerulonephritis, acute diffuse glomerulonephritis, and disseminated lupus erythematosus.

Neither the clinical findings associated with secondary syphilis nor a positive serologic test for syphilis was present in this case. Although the complications of pregnancy cannot be considered in the differential diagnosis here, I should mention that hypoproteinemia, proteinuria and edema may occur during the last trimester of pregnancy, possibly the result of a pre-existing and latent nephrotic state.

Amyloidosis is a tempting diagnostic possibility. However, the protocol does not suggest any of the causes of secondary amyloid disease such as bronchiectasis, osteomyelitis, tuberculosis, rheumatoid spondylitis, multiple myeloma and syphilis. A biopsy of the liver or kidney would be helpful here and certainly more informative than the Congo red test. Some believe that primary amyloidosis and secondary amyloidosis are the same disease.

The patient did not have glycosuria or any other evidence of diabetes mellitus. This, together with the normal fundi and normal blood pressure, speaks against intercapillary glomerulosclerosis, a complication of long-standing diabetes.

Thrombosis of the renal veins should be considered, although it is a rare condition and is not commonly diagnosed before death. It may not be clear even at autopsy whether the thrombosis is the cause or the result of the nephrotic state, since venous thromboses are commonly seen in adults afflicted with this syndrome. Collateral abdominal veins with upward blood flow would suggest thrombosis of the renal veins. Venography of the inferior vena cava or renal veins often is required in order to recognize the disease.

Membranous glomerulonephritis and acute glomerulonephritis are good diagnostic possibilities. The patient's allergic diathesis supports this contention. However, there is no indication of contact with trimethadione or related compounds, or with gold, calomel or bismuth, substances whose use is followed occasionally by the nephrotic syndrome. Moreover, there is no evidence of a previous infection with beta hemolytic streptococci. (Antistreptolysin-O titers and throat cultures are not mentioned in the protocol.)

Thus, by a process of elimination, I am directed to the final diagnostic possibility, disseminated lupus erythematosus, which I feel best fits this case. The multiple-system involvement, repeatedly negative blood cultures in the face of intermittent febrile episodes, and poor response to therapy are confirmatory. I would feel better about the diagnosis if the patient had had a rash, involvement of joints, or a positive L.E. preparation, but these are not essential.

The hospital course seems more interesting and challenging than the diagnosis of the underlying disease. Despite intensive antibiotic therapy, the administration of nitrogen mustard and massive doses of corticosteroids, the patient died after one month in the hospital. I would like to consider the natural course of disseminated lupus erythematosus in the light of the terminal events. In this disease, death may result from extensive involvement of important organ systems such as the kidneys, brain, lungs and blood. Severe renal disease with progressive uremia was an important feature of this case and may have caused death. Another possibility is a major thrombo-embolic episode, which commonly occurs in the nephrotic syndrome. Recently the manifestations of lupus erythematosus that affect the central nervous system have been re-emphasized; toxic delirium, convulsions and coma have been described. One should suspect cerebral involvement in any case in which massive hormone therapy such as was employed here has no effect on fever and toxicity. Before antibiotics, ACTH or corticosteroids were available, many patients with disseminated lupus erythematosus died of bacterial infections. Occasionally, tuberculosis was responsible, and less commonly the fungi. Such infections were attributed to the debilitation and lowered resistance of these chronically ill patients, to alterations in their serum globulins, and to the severe leukopenia seen in a few of them. Moreover, infections were known to be particularly

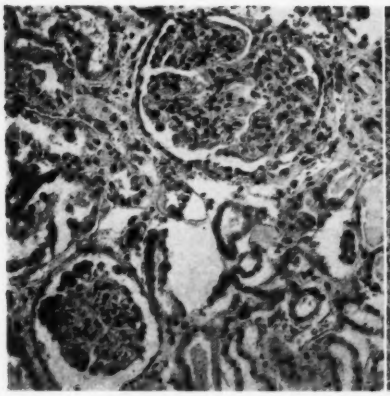

FIGURE 1. Photomicrograph showing proliferative glomerulitis with fusion of the tufts to the capsule. Fibrosis is present.

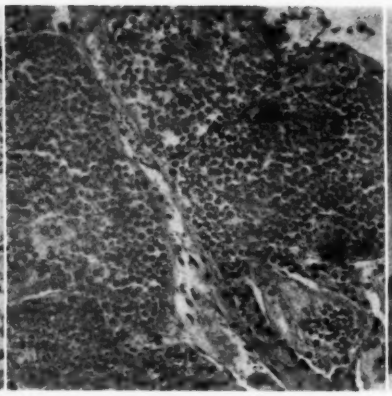

FIGURE 2. Pure colonies of *Cryptococcus (Torula)* without any host reaction.

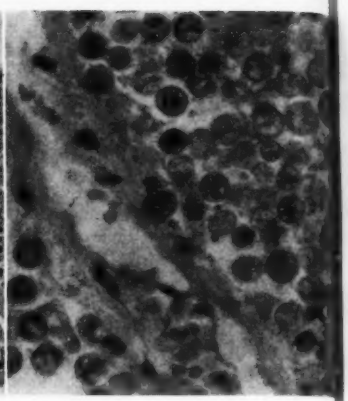

FIGURE 3. Higher power view showing pure colonies of *Cryptococcus (Torula)* without any host reaction.

hazardous in the nephrotic syndrome, whatever the cause.

Antibiotic and hormonal therapy has complicated the problem of infection in disseminated lupus erythematosus. Empirical use of multiple antibiotics often has resulted in elimination of sensitive organisms and emergence of resistant bacterial strains as well as overgrowth of fungi in areas of the body where they usually are not so evident. The protocol of this case illustrates this well; organisms normally found in the bowel were cultured from the mouth, and oral monilial infections were troublesome. The large dosages of corticosteroids given during the final period of hospitalization might well have contributed to the dissemination of some infectious agent, possibly the tubercle bacillus. However, tuberculosis does not seem likely in view of the streptomycin therapy given. The negative blood cultures speak against other bacterial infections, specifically due to *Esch. coli* or *Str. faecalis*, the organisms cultured from the mouth. I think, therefore, that this man had disseminated lupus erythematosus manifested primarily as the nephrotic syndrome and complicated by a terminal fungous infection. In my opinion a monilial infection is the best possibility, entering the respiratory tract from the mouth and subsequently becoming generalized with abscesses occurring anywhere in the body. Whether such a terminal infection would be a part of the natural course of the underlying disease or the result of antibiotic or corticosteroid therapy is problematical.

Pathologic Report

DR. LEONARD HURLEY (pathologist): The one thing we withheld from the protocol was the positive lupus erythematosus preparation in the outside hospital, or possibly a number of them, but obviously we would not mention them. I was gratified to see that no one attempted to tie in the symptom of everything tasting "awful" with the flora found in the oral cavity.

Postmortem examination showed the body of a well-developed white man with a typical moon face, periorbital swelling, and marked pitting edema of the lower extremities. Petechial hemorrhages were scattered over the skin of the thorax and abdomen. There was a bilateral hydrothorax, the pleural cavity containing approximately 500 cc. of clear straw-colored fluid. Marked fibrous adhesions surrounded the entire right lung. The peritoneal cavity contained about 2500 cc. of clear yellow ascitic fluid.

The heart weighed 450 gm., and grossly it resembled what we call an old healed rheumatic heart—heart disease of minimal degree. There were focal areas of milk patches over the epicardium. Grossly the fibrous strands throughout the myocardium appeared to be increased, and the mitral valve was mildly involved with some thickening and minimal

e.usion. It did not appear that this was a functional valvulitis or in any way deleterious to the patient. The left ventricular wall was very slightly hypertrophic.

The lungs, combined, weighed approximately 1500 gm. There was a heavy pleuritis over the right lung. Multiple abscess cavities were seen bilaterally, filled with a necrotic material gray to yellow in color. The same substance completely replaced the mediastinal and celiac lymph nodes, obliterating the normal architecture of the nodes.

The liver weighed 3200 gm. and was studded throughout with necrotic gray material, irregular in outline, with a peripheral hemorrhagic zone. The spleen weighed 190 gm., and again there were irregular areas of gray necrotic tissue, blending rather subtly with the surrounding splenic tissue. Grossly it appeared that this necrotic tissue had replaced about one-third of the normal spleen. The right kidney weighed 300 gm., the left 330 gm., and they were grossly normal except for the obvious increase in size and weight. The surface was smooth and there was no mottling of yellow or red tissue. The adrenal glands appeared rather atrophic on gross inspection. There was no evidence of meningitis or purulent material or any abnormality of the central nervous system.

The photomicrograph in figure 1 shows obvious glomerulitis, with fusion of the individual capillary tufts, a thickened and fibrotic Bowman's capsule, increased cellularity and epithelial cell proliferation, but empty periglomerular space—no cellular debris. The blood vessels in the surrounding area appear normal. They are not thickened, the tubules are well preserved, and there is no evidence of increased cellularity in the interstitial tissue. This section at least represents pure glomerulitis of a proliferative type.

A photomicrograph of the lung (figure 2) reveals the alveoli that were making up dense consolidations to be filled with *Cryptococcus*, or *Torula*, as it has been called, without any cellular reaction—just pure colonies of *Cryptococcus*, no reaction from the host.

The photomicrograph in figure 3 is a higher power view, and it shows nothing but *Cryptococcus*. This is rather a resting stage, but on searching long enough you can find simple budding which is consistent with the *Torula*. A higher power view under oil showed large rods typical of coliform organisms or anaerobic bacilli mixed intimately with the *Cryptococcus* organisms and the bacilli.

A section through the adrenal gland showed marked atrophy. The zona glomerulosa was practically gone. A little fasciculata was left, the reticularis was largely necrotic, and the medullary center was relatively increased because of the atrophy of the cortical width.

To summarize this case, clinically it was diagnosed disseminated lupus erythematosus, and the patient was treated with massive doses of corticosteroids and antibiotics. The lungs, liver, spleen and lymph nodes were involved by *Cryptococcus* or *Torula* abscesses; there was no involvement of the central nervous system, which is quite unusual. We had a number of sections through meninges in various areas and there was no inflammation at all. The third condition diagnosed was subacute glomerulonephritis, obviously diffuse and histologically nonspecific.

If we agree, then, that lupus erythematosus is a disease that is diagnosed clinically and occasionally can be diagnosed by tissue study but not exclusively so, then this is such a case. If someone wants to question the diagnosis of lupus, it will be between him and the clinician. There were positive L.E. preparations, but I do not believe they are absolutely pathognomonic of the disease, although they certainly point to it. In my mind, I do not doubt that this is disseminated lupus with protean manifestations, as Dr. Poske went over very well, and the glomerulonephritis, I think, is entirely consistent with a case in which the patient dies in uremia with a lupus nephritis. But the histologic picture is not typical, from what I can read on it. Allen has stated that 60 per cent of all disseminated cases show a typical wire-loop kidney. This case does not. In summary, it is a case of systemic lupus erythematosus with complications which resulted from steroid and antibiotic therapy and extreme debility, ending in death from a fungous infection associated with uremia from renal failure.

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"JOURNEY'S END" OR "THE ULTIMATE ADVENTURE"

THE title of this editorial embodies the titles of two essays on the subject of death—the first by Sir Heneage Ogilvie,[1] the second by the late James P. Warbasse.[2] Far too seldom do philosophical essays of such merit come from the pens of physicians. Yet from the fact that no one else but the physician has greater intimacy with the aspects of death, no one else is better able to discuss it. Sir Heneage notes that people face death in a manner dependent on the extent to which they have achieved their objectives in life:

"The courageous and educated man, when he comes to realize that the time left to him must be measured in days or at most weeks, tends to depart a little from his accustomed modesty. He knows that for a brief period he is the chief actor in the most powerful drama of human experience. He knows that he is being studied with attention and, he hopes, with respect and affection. He would like his departure to be dignified. He would like to think that it will be remembered."

Similarly Dr. Warbasse said, "The aged person, knowing he is approaching death, should not have to turn away from the event as though it were shameful or subject for taboo. He should be free of discomforts—that is his doctor's duty. Then, there yet remains for him something to be found in this greatest of adventures into eternity. First, there is the satisfaction of equanimity. I have seen a dying man who was the only person in the family possessed of sweetness and calm, impressing me as a beautiful sight."

Many descriptions—actual and imaginary—have been published descriptive of death or the feeling of impending dissolution. Sir Heneage says, "The sensation of dying is usually a consciousness that the heart is faltering in its task of supplying blood to limbs and brain, and that the brain will soon cease to hum with the thoughts and beliefs, the memories of the past and the hopes for the future, that represent us to ourselves and the world. But very soon the anoxia leads to a dullness of perception, a disorientation of ideas, a retreat from the hopes and fears of the live world to the make-believe of a world of fantasy."

Dr. Warbasse too described the physiology of death:

"We must bear in mind that death, commonly recognized as the cessation of heart beat and respiration, is usually caused by constitutional changes producing toxins which paralyze the circulatory and respiratory centers at the base of the brain. Before the two

vital centers have become paralyzed, the intellectual centers of the forebrain are usually dulled. The mind is enveloped in the cloudiness of approaching loss of function, so that death is commonly preceded by a period of unconsciousness."

More recently Ian Grant,[3] a general practitioner of Glasgow, presented to the British Medical Association at its 1957 annual meeting some thoughts on the "Care of the dying":

"The phrase death agony is, I think, ill chosen. In the ordinary way death comes peacefully or, if not, can easily be made so by sedative and analgesic drugs. Relatives should not try to call back into activity a mind that is fitfully wandering, and, above all, there should always be present a good nurse—not necessarily a trained nurse—able and willing to give every comfort to the patient."

In his superb essay, Sir Heneage speaks of the famous words uttered, or said to have been uttered, by distinguished men of the past. William Hunter rose from a sickbed to deliver a lecture and fainted away at the end. After he recovered consciousness he whispered, "If I had strength to hold a pen, I would write how easy and pleasant a thing it is to die." Sir William Osler on his deathbed said, "I have been too far across the river to go back and have it all over again." A bishop, waking in the night with a sense of floating away, thought to himself how he must look in the morning, being found dead. He decided that the appropriate position would be on his back with his arms crossed over his breast. Later he wrote that he took this posture but "Nothing happened, and my arms getting cold, I put them back under the coverlet and went to sleep."

Sir Heneage discusses euthanasia and holds personally "that euthanasia puts the doctor in the dangerous position of judge, jury, and executioner all in one." He believes that the hospital is usually the best place for the elderly patient who is seriously ill but may recover. For one who is dying, the best place, or at any rate the happiest place, he says, is his own home. All experts agree that the dying have a right to the relief of pain. The loneliness of death is its most fearsome aspect and the doctor can render a great service by assuring the patient that he is with him, holding his hand at his departure. "At such a time," says Sir Heneage, "optimism is the greatest analgesic; hope is the most certain tranquilizer."

Dr. Grant is especially concerned by current attitudes toward the extremely aged or senile person. "There are times," he says, "when I have less and less sympathy with the superhuman efforts merely to extend life in old age. . . . It is our duty to preserve not only health and life but also the joy of living, and often as a G.P. when dealing with cases of complete senility, when both mind and body have long since served their day and generation, one wonders whether one should really strive officiously to keep alive by the use of antibiotics, blood transfusions and intravenous injections of varying potency, or whether we should not let nature take its course and let the weary pass quickly into eternal rest."

Dr. Grant discusses especially the care of those with cancer, tuberculosis, congestive heart-failure, chronic rheumatism and cerebral thrombosis. Many lonely old people still suffer from malnutrition and associated deficiency diseases.

The general practitioner has a dual problem—the care of the dying and the care of their relatives. "How often do we see devoted mothers and dutiful daughters sacrificing their health and strength in attendance on a loved one."

Dr. Grant concludes: "Let us visit our dying patient as often as we can find time, but we should never discuss a patient's progress with relatives when in the sickroom. So often a patient may appear to be unconscious, but he or she may overhear an expression of opinion which, to one who is gravely ill, may cause added distress and anxiety. Let us remember that although we may be able to do little for the patient our visit is of inestimable help to anxious relatives and we can thereby make their duties a little less burdensome."

MORRIS FISHBEIN

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2. Warbasse, J. P.: The ultimate adventure. Geriatrics 11:468-470 (October) 1956.
3. Grant, I.: Care of the dying. Brit. M. J. 2:1539-1540 (December 28) 1957.

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES

UNDER the sponsorship of the Association of American Medical Colleges, the American Medical Association, the American Hospital Association, and the Federation of State Medical Boards of the United States, an Educational Council for Foreign Medical Graduates has been established with offices at 1710 Orrington Avenue, Evanston, Illinois. Among the functions of this Council will be the distribution to foreign medical graduates of authentic information regarding the opportunities, difficulties and pitfalls involved in coming to the United States with the hope of becoming licensed to practice, as an exchange visitor or student who wishes to have an internship or residency in a United States hospital. The Council will also develop certification for properly qualified graduates of foreign medical schools indicating that their educational credentials have been checked and found to meet the minimal standards of the United States, that their command of English has been tested and found adequate, and that their general knowledge of medicine as evidenced by passing an examination, known as the American Medical Qualification Examination, is adequate to permit them to assume an internship in an American hospital. The Council will also provide hospitals, state licensing boards and specialty boards, which the foreign medical graduate may designate, with the results of their studies of the graduate's qualifications.

In a preliminary statement, the Council indicates also that it will not serve as a placement agency, evaluate teaching programs of foreign medical schools, or intercede for foreign physicians in their problems with state medical boards or specialty boards.

Each of the sponsoring organizations will appoint two members to the board and two representatives will be selected at large—one from the Department of Defense and one from the Department of Health, Education and Welfare. The first board is headed by Dr. J. Murray Kinsman, dean of the University of Louisville School of Medicine, as president and Dr. Dean F. Smiley as executive director.

The board is contemplating conducting two examinations annually with questions selected from the National Board of Medical Examiners' pool of questions. The National Board of Medical Examiners will use its presently constituted examination centers in the United States and will also establish examination centers abroad to meet developing needs. A charge of $50 is to be made to foreign medical graduates to cover the cost of the screening which will include $15 for the evaluation of credentials and $35 for the American Medical Qualification Examination. Foreign medical graduates who are abroad will be billed the $50 only when they pass the screening, receive a position in an American hospital, or are in some other manner earning American dollars. Any American hospital which receives a candidate who has been screened will be billed $75 for each candidate accepted.

At present, the first American Medical Qualification Examination for foreign medical graduates already in this country has been held (late winter 1958). The first examination abroad and the second American examination will be in August or September 1958. Anyone especially interested may write to the Evanston office for a brochure which gives full information.

MORRIS FISHBEIN

MEDICAL EDUCATION WEEK

FOR the third successive year leading organizations concerned with medical education are cooperating in the celebration of a medical education week, April 20 to 26. The chief purpose is to interest the public in the problems that prevail and to gain public support in meeting the challenges of the future. In furtherance of this objective, a fact sheet has been prepared which provides accurate information on the present status of medical schools, their faculties and facilities.

Medical schools now number 83, including four which have only a two year basic medical program. The University of Florida and Seton Hall University have established new four year schools which will not, however, be eligible for

approval until their first classes graduate in 1960. Another four year school will begin in Kentucky in 1959. The total number of students enrolled is 29,003, with 127 additional students at Florida and Seton Hall. The number of graduates has increased from 4,565 in 1930 to 6,796 in 1957.

Most physicians can remember the period immediately after the war when there were four applicants for each place available in a freshman class. The number of applications decreased from 24,434 in 1950 to 14,538 in 1954. At present about two applicants are inquiring for each place available. The impression that there were 10 applicants for each place was due to the fact that each applicant was applying to three or four schools, fearing failure to be accepted. The current swing to other sciences and professional areas seems to be related to increased publicity for electronics, nuclear energy, space travel and similar subjects. Moreover, the increased costs of medical education and the duration of training tend to turn students to other fields.

More than 300 additional places in freshman classes have been created by existing schools during the past five years. No doubt improved facilities will offer more opportunities than now exist. However, any large increment will depend on the establishment of still more medical schools. At its annual meeting in 1956 the Association of American Medical Colleges urged an increase in the number of schools. The physician-population ratio is now 133 doctors to 100,000 people. Our population is rising sharply. The number of the aged and those with chronic diseases is steadily increasing. Full-time positions in medical services and particularly in governmental agencies are becoming more numerous. More hospitals are being built in small communities. The growth of hospitalization and medical care insurance programs has been amazing in its rapidity and scope. In 1957 the Association of American Medical Colleges and the Council on Medical Education and Hospitals of the American Medical Association agreed to encourage universities to establish new programs in medical education which will offer the first two years of the four year medical course. No doubt such courses in time will evolve into complete medical schools.

Practically all medical schools require a minimum of three years of college study for entrance. In 1955 to 1956, of all freshmen in medical schools, 75 per cent had four years of college education and 70 per cent had baccalaureate degrees. The number of students entering medical schools with a grade A average has decreased from 40 per cent in 1950 to 16 per cent in 1956; the number of students with a grade B average has increased from 43 to 70 per cent in the same period. The number with a grade C average has declined from 17 to 14 per cent. Medicine still is not a career for a lazy, inept or unwilling student.

Medical schools are concerned with maintaining standards that will bring into medical practice men of the highest character and integrity, men of good intellect motivated toward a scientific career, and men whose lives are animated by a philosophy of service. The rewards of achievement in medicine are not surpassed by those of any other occupation.

MORRIS FISHBEIN

WORLD HEALTH DAY

ON April 7 the World Health Organization celebrated 10 years since its constitution first went into force. Eighty-eight nations now hold membership in this joint effort to raise the health standards of the world. The tremendous improvement in human health, which reflects the advance of knowledge during the last 100 years, is immediately apparent. The last 50 years truly represent the golden age of medicine. Yet even 10 years have made a great difference—because the intensity and speed of progress are now so great that hardly three months can pass without some significant announcement in the field of world health.

Death rates from tuberculosis are steadily declining throughout the world, but this disease is still the greatest killer of all infectious and parasitic diseases. Although enough is known to permit the stamping out of malaria, three-fourths of mankind live in malaria zones. During the last 10 years, both incidence and

death rates have been cut by 30 per cent, but this disease is still one of the world's greatest problems. As an example of the scope of operations of the World Health Organization, 74 million persons have been vaccinated against tuberculosis with BCG from 1948 to 1957.

One of the great concerns of WHO is the supply of qualified medical care. Fourteen countries have one physician for every thousand or fewer persons; at the opposite extreme are 22 countries which have one physician for 20,000 or more inhabitants. Estimates indicate that 1,236,000 physicians now serve the world's 2.7 billion people, and 638 medical schools in 85 countries annually graduate 67,000 new physicians. Only nine countries have one medical school for less than one million population. In 13 countries there is only one medical school for from 9 to 17 million people.

From May 26 to June 14 the first meeting of the World Health Organization to take place in the United States will be held in Minneapolis. The occasion may well serve to stimulate and inspire renewed interest of all Americans in the cooperative effort needed to attain the greatest possible success in overcoming disease and disability.

MORRIS FISHBEIN

LEGAL ASPECTS OF ARTIFICIAL INSEMINATION

ALTHOUGH official records are unavailable, evidence indicates that anywhere from 50 to 200,000 "test-tube" babies have been born in the United States. In 1945 a symposium[1] on artificial insemination was held under the cosponsorship of the Institute of Medicine of Chicago and the Chicago Bar Association. At that time Dr. J. P. Greenhill emphasized the necessity for clarifying the legal aspects of this procedure. He said, "Should the courts decide, however, with some degree of unanimity, that artificial insemination of a woman with a donor's semen constitutes adultery, then we physicians will have to discontinue performing this procedure." Recently the Scottish Court of Session[2] ruled in a hearing on an action for divorce that artificial insemination from a donor does not constitute adultery. A woman who had not lived with her husband for more than a year gave birth to a child and claimed that it had been born as the result of artificial insemination through a donor. The husband maintained that he had never agreed to this. Lord Wheatley pointed out that there were manifestly grave moral, ethical, social and personal considerations involved in artificial insemination. The court was concerned only with whether or not the act constituted adultery in its legal meaning. *Lancet* comments, "Lord Wheatley's view that there cannot be adultery without actual sexual intercourse is in line with English judgments on the nature of adultery. Thus manual gratification by a wife of another man's sexual organs has been held not to be adultery, although a breach of the obligations of marriage."

In the *Journal of Forensic Medicine*, Dr. Levisohn[3] recently has considered this subject from many points of view. Dr. J. Marion Sims, he points out, performed artificial insemination in the United States in 1866. He recognizes that the chief opposition to the procedure at present is based on religious rather than biologic grounds. Apparently legislative bodies have not yet taken action on the subject in any country. However, the law invariably follows scientific discovery and seldom, if ever, anticipates it. A court in Ontario in 1921 ruled that artificial insemination is in itself "sexual intercourse." Dr. Levisohn cites a number of other legal decisions, in each instance complicated by extraneous economic or social factors. Obviously the time is near for consideration of legislation to define the terms used, the limitations that may be imposed, and the obligations that ensue from artificial insemination. Biologists and physicians have demonstrated adequately the effectiveness of the process in securing the birth of a child.

MORRIS FISHBEIN

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2. EDITORIAL: Artificial insemination not adultery. Lancet 1:157 (January 18) 1958.
3. LEVISOHN, A. A.: Dilemma in parenthood; sociolegal aspects of artificial insemination. J. Forensic Med. 4:147-172 (October-December) 1957.

Documentary Case History . . .

Hypertension controlled for four years with Serpasil®

(reserpine CIBA)

K. C., a 67-year-old retired shirt manufacturer, had a 16-year history of hypertension, was troubled by recurrent dizzy spells and headaches. "I'd get several attacks a day. . . . Usually I'd go into the bedroom and lie down." Serpasil therapy was started four years ago, effecting a gradual reduction of the patient's initial blood pressure of 220/120 mm. to the present 140/80. Now well and asymptomatic, ". . . I'm able to go to matinees and see some of the TV shows."

SUPPLIED: TABLETS, 4 mg. (scored), 2 mg. (scored), 1 mg. (scored), 0.25 mg. (scored) and 0.1 mg.

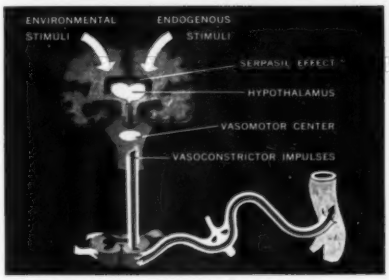
ELIXIRS, 1 mg. and 0.2 mg. Serpasil per 4-ml. teaspoon.

PARENTERAL SOLUTION: *Ampuls*, 2 ml., 2.5 mg. Serpasil per ml. *Multiple-dose Vials*, 10 ml., 2.5 mg. Serpasil per ml.

Hypertension controlled through

SYMPATHETIC REGULATION

Serpasil shields the psychic and somatic reaction centers from emotional and environmental stress stimuli, thereby inhibiting the discharge of vasoconstrictive impulses through the sympathetic nerves.



Adapted from Moyer, J. H., Dennis, E., and Ford, R.: Arch. Int. Med. 96:530 (Oct.) 1955.

CIBA SUMMIT, N. J. 2/2553MK

New *for your armamentarium*

Information published in this department is supplied by the manufacturers of the products described.

• KENACORT®

PURPOSE: To provide corticosteroid therapy.
COMPOSITION: The 9-alpha-fluoro-16-alpha-hydroxy derivative of prednisolone.
INDICATIONS FOR USE: Allergic, inflammatory and dermatologic conditions.
CAUTION: Like other potent gluco-corticoids, this drug should be used under close clinical supervision. It does not, however, cause sodium retention, so the usual criteria for cortisone overdosage (gain in weight, clinical edema and hypertension) do not apply.
HOW SUPPLIED: 1 mg. tablets in bottles of 50 and 500; 4 mg. tablets in bottles of 30 and 100.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corp., New York.

• ISUPREL® MISTOMETER

PURPOSE: To relieve bronchospasm.
DESCRIPTION: This pocket-size, metered-dose aerosol dispenser is a completely self-contained unit, yet is small enough to be concealed in the hand. It consists of a 10 cc. vial of the bronchodilator Isuprel hydrochloride (isoproterenol), 0.25 per cent aerosol solution, plus a detachable plastic mouthpiece with built-in nebulizer and protective cap. Pressure on the bottle releases through the mouthpiece an exact amount of aerosol mist of optimal particle size. The unit delivers about 200 oral inhalations and is precision engineered to prevent leaking, waste or blockage.
INDICATIONS FOR USE: Asthma, chronic bronchitis and pulmonary emphysema.
PRODUCER: Winthrop Laboratories, New York.

• NEBULIZER

DESCRIPTION: Generating particles in the effective therapeutic range of 0.5 to 3.0 μ, this nebulizer has flow rates as low as 3 l. per minute and as high as 15 l. per minute at normal pipeline pressure. A warning whistle registers any obstructions in the outlet tubing, and a special reducer provides either small, smooth-bore or large corrugated inhaler tubing. The nebulizer may be attached directly to a flowmeter or to a wall outlet. It serves as a humidifier when water is placed in it and air or oxygen is used as the propelling force. Featuring a nonbreakable plastic bottle and noncorrosive metallic body, it requires little maintenance. A liquid strainer, removable for cleaning, prevents obstruction of the nozzle.
PRODUCER: Ohio Chemical & Surgical Equipment Co. (A division of Air Reduction Company, Inc.), Madison, Wis.

(Continued on page A-130)

What is a Sensible Breakfast During the Growth Years?

Children who eat nutritious breakfasts regularly are more likely to be well nourished than those with poor breakfast habits.* This important finding emphasizes the long-known relationship between nutritious breakfast meals and the performance level of school children.

A sensible breakfast for most children is one which supplies ample energy for a full morning's work and play; which provides ample growth-promoting protein, vitamins, and essential minerals; which is tasteful, easy to digest, and is eaten in a pleasant atmosphere; but which does not burden the digestive tract unduly or overload the food capacity of the child.

A dish of oatmeal provides nutritional advantages few foods can exceed. It contains more protein and more thiamine than other whole grain cereals. In addition, it contributes other B vitamins and is outstanding for its iron content.

A steaming bowl of oatmeal is a dish welcomed by children. It reflects a warm, secure home atmosphere. It means a pleasant, satisfying meal with which to start the day's work and play.

Quaker Oats and Mother's Oats, the two brands of oatmeal offered by The Quaker Oats Company, are identical. Both brands are available in the Quick (cooks in one minute) and the Old-Fashioned varieties which are of equal nutrient value.

*Martin, E.A.: Roberts' Nutrition Work with Children, Chicago, The University of Chicago Press, 1954, pp. 141-146.

The Quaker Oats Company
CHICAGO

• DURA-TAB SM QUINIDINE GLUCONATE

PURPOSE: To provide sustained treatment for cardiac therapy.
COMPOSITION: Each tablet contains 5 gr. quinidine gluconate.
INDICATIONS FOR USE: Premature auricular, nodal and ventricular contractions; auricular tachycardia, flutter and fibrillation (established and paroxysmal and ventricular tachycardia); and night cramps.
DOSAGE AND ADMINISTRATION: For conversion of auricular fibrillation to normal rhythm, 2 tablets three to four times daily for two or three days. For maintenance, 1 or 2 tablets administered at 10 to 12 hour intervals.
HOW SUPPLIED: Bottles of 30 and 100.
PRODUCER: Wynn Pharmacal Corporation, Philadelphia.

• DESITIN® BABY LOTION

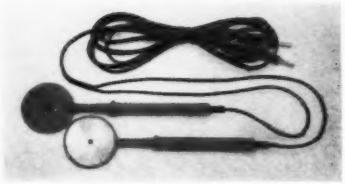
PURPOSE: For over-all care of the infant's skin.
COMPOSITION: Liquid lanolin, hexachlorophene, vitamins A and E, cleansing emulsifiers and wetting agents.
DESCRIPTION: Greaseless and stainless, the lotion soothes and lubricates the skin, protects against certain common skin bacteria, and cleanses thoroughly (without mineral oil).
DOSAGE AND ADMINISTRATION: Apply after each diaper change and over entire body after bath.
HOW SUPPLIED: 4 oz. bottles.
PRODUCER: Desitin Chemical Company, Providence, R. I.

• NEOCYLONE®

PURPOSE: To control rheumatism.
COMPOSITION: Each tablet contains:

Prednisolone	2 mg.
Potassium salicylate	0.28 gm.
Potassium para-aminobenzoate	0.30 gm.
Ascorbic acid	20 mg.

INDICATIONS FOR USE: Rheumatoid arthritis, acute rheumatic fever and gout.
CAUTION: Since some of the usual warning signs of corticoid excess (edema, hypertension, etc.) may not appear, precautions common to other gluco-corticoids should be observed. This drug is contraindicated in cases of active tuberculosis or peptic ulcer, psychotic and prepsychotic states, fresh intestinal anastomoses, and herpes simplex of the eye, and within the first 24 hours of sulfonamide therapy; it should be used with care in cases of renal insufficiency.
DOSAGE AND ADMINISTRATION: 4 to 8 tablets daily in divided doses, preferably after meals and at bedtime. Reduce dosage to optimal maintenance level with improvement.
HOW SUPPLIED: Bottles of 50, 100 and 500.
PRODUCER: The Central Pharmacal Company, Seymour, Ind.



• DEFIBRILLATION ELECTRODES

DESCRIPTION: Designed for use with any make or model of electric defibrillators, these stainless steel concave electrodes are large in area to provide for greater contact and are fully insulated against accidental shock. The cords as well as the electrodes can be autoclaved.
PRODUCER: The Birtcher Corporation, Los Angeles.

• SYNTUSSIN

PURPOSE: To relieve cold symptoms.
COMPOSITION: Chlorpheniramine maleate, phenylephrine hydrochloride, dextromethorphan hydrobromide and terpin hydrate, in tablet form.
INDICATIONS FOR USE: Nasal congestion, cough and other upper respiratory infections.
DOSAGE AND ADMINISTRATION: 2 tablets initially and 1 tablet every three or four hours as needed.
HOW SUPPLIED: Bottles of 48.
PRODUCER: Ives-Cameron Company, Philadelphia.

• PENITE TABLETS

PURPOSE: To prevent angina pectoris attacks.
COMPOSITION: Each tablet contains 0.3 mg. nitroglycerin (1/200 gr.), 10 mg. pentaerythritol tetranitrate and 0.07 mg. reserpine.
CAUTION: As with all nitrates, this drug is contraindicated for patients with anemia or glaucoma.
DOSAGE AND ADMINISTRATION: 1 tablet swallowed before each meal, and 1 at bedtime if necessary.
HOW SUPPLIED: Bottles of 100.
PRODUCER: G. W. Carnrick Company, Newark.

• PARAFLEX®

PURPOSE: To relieve muscle spasm.
COMPOSITION: Each tablet contains 250 mg. of chlorzoxazone (5-chlorobenzoxazolinone).
INDICATIONS FOR USE: Arthritic, rheumatic, traumatic and orthopedic disorders.
CAUTION: Side effects are rare and usually mild, although gastrointestinal or central nervous system reactions may be seen occasionally.
DOSAGE AND ADMINISTRATION: 1 or 2 tablets taken three times a day.
HOW SUPPLIED: Bottles of 50.
PRODUCER: McNeil Laboratories, Inc., Philadelphia.

(Continued on page A-132)

In urinary-tract infections

HIGH TISSUE LEVELS

HIGH BLOOD LEVELS

LOW TOXICITY

SUSPENSION TABLETS

SULFOSE®

Triple Sulfonamides, Wyeth

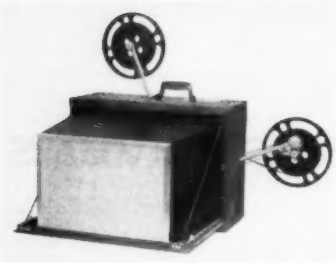
(*Sulfapyrimidines: Sulfadiazine, Sulfamerazine, Sulfamethazine*)

Wyeth®

Philadelphia 1, Pa.

...ICIANS' COUNCIL ...ATION ON CHILD HEALTH

...s advertisement con-...s to the Code for ...rtising of the Physi-...' Council for Infor-...tion on Child Health.



• PROFESSIONAL TWO-IN-ONE PROJECTOR

DESCRIPTION: Featuring a built-in 18 by 13 in. screen, made possible by the wide-angled 14 mm. lens, this 16 mm. sound motion-picture unit may be used for both front and rear projection. The unbreakable translucent plastic screen gives an unusually wide viewing angle and an extremely sharp image. Black shielding on all four sides of the light beam prevents any ambient light from dulling the image, producing excellent picture contrast, even in a fully lighted room. A Bell & Howell Filmosound 385 optical-sound 16 mm. mechanism and 15 W amplifier are incorporated in the unit. The 8 in. speaker, positioned in the projector case so that during rear projection the sound comes from behind the screen, is removable for placement where desired during front projection. The unit is furnished with a 750 W lamp, has 1000 W capacity, and will accommodate 2000 ft. reels. Front projection on larger screens is arranged by swinging the mirror out of the light beam and replacing the lens with one of 2 in. focal length. A multiple-purpose automatic shut-off switch stops the projector when the show is completed, the lower film loop is lost, or when torn sprocket holes or faulty splices pass through the mechanism, making film inspection easier. The unit is housed in a gray, plastic-covered case measuring 18 by 10 by 25 in. Optional equipment includes an 18 by 24 in. rear-projection screen, a 2 in. Bell & Howell Super Proval lens for front projection, and a Filmosound 302 magnetic recording-projector mechanism.
PRODUCER: Triangle Projectors Inc., Skokie, Ill.

• COSA-TETRACYN®

PURPOSE: To provide oral antibiotic therapy.
COMPOSITION: Tetracycline hydrochloride with glucosamine.
INDICATIONS FOR USE: Infections caused by gram-positive and gram-negative bacteria, *Rickettsia*, certain spirochetes, large viruses and protozoa.
DOSAGE AND ADMINISTRATION: Orally, with 8 oz. of water, as prescribed by physician.
HOW SUPPLIED: 125 mg. capsules in bottles of 25 and 100, and 250 mg. capsules in bottles of 16 and 100.
PRODUCER: Pfizer Laboratories Division, Chas. Pfizer & Co., Inc., Brooklyn.

• MYCIFRADIN® N

PURPOSE: To prepare bowel prior to operation involving lower intestinal tract.
COMPOSITION: Each tablet contains 0.5 gm. neomycin sulfate and 125,000 units of nystatin.
DESCRIPTION: The compound provides rapid antibacterial action, elimination of yeasts and fungi in the intestinal tract, and specific antifungal prophylaxis against monilial growths sometimes associated with antibiotic therapy. As a result, a surgical field virtually free of the normal bacterial flora is secured. Other advantages include: a more pliable intestine which facilitates surgical manipulation; minimized hazard of possible spillage of bowel content; less risk of peritonitis or wound infection, or both; and rapid action, whereby the patient can be prepared for operation in four hours.
DOSAGE AND ADMINISTRATION: 2 tablets orally every four hours for a total of 12 tablets.
HOW SUPPLIED: Bottles of 20, 100 and 500.
PRODUCER: The Upjohn Company, Kalamazoo, Mich.

• DESITIN® ACNE CREAM

PURPOSE: To remove excess skin oiliness and to clear clogged sebaceous gland openings.
COMPOSITION: Zinc oxide, superfine sulfur, resorcinol and hexachlorophene in a flesh-colored, greaseless and fast-drying base.
DOSAGE AND ADMINISTRATION: Wash affected areas thoroughly with mild soap and water, then apply a thin layer of cream once daily and at bedtime.
HOW SUPPLIED: 1½ oz. tubes.
PRODUCER: Desitin Chemical Company, Providence, R. I.

• PHENERGAN® EXPECTORANT PEDIATRIC

PURPOSE: To control cough.
COMPOSITION: Each teaspoonful (5 cc.) contains:

Dextromethorphan hydrobromide	7.5 mg.
Promethazine hydrochloride	5 mg.
Fluid extract ipecac	0.17 min.
Potassium guaiacolsulfonate	44 mg.
Chloroform	0.25 min.
Citric acid	60 mg.
Sodium citrate	197 mg.
Alcohol	7%

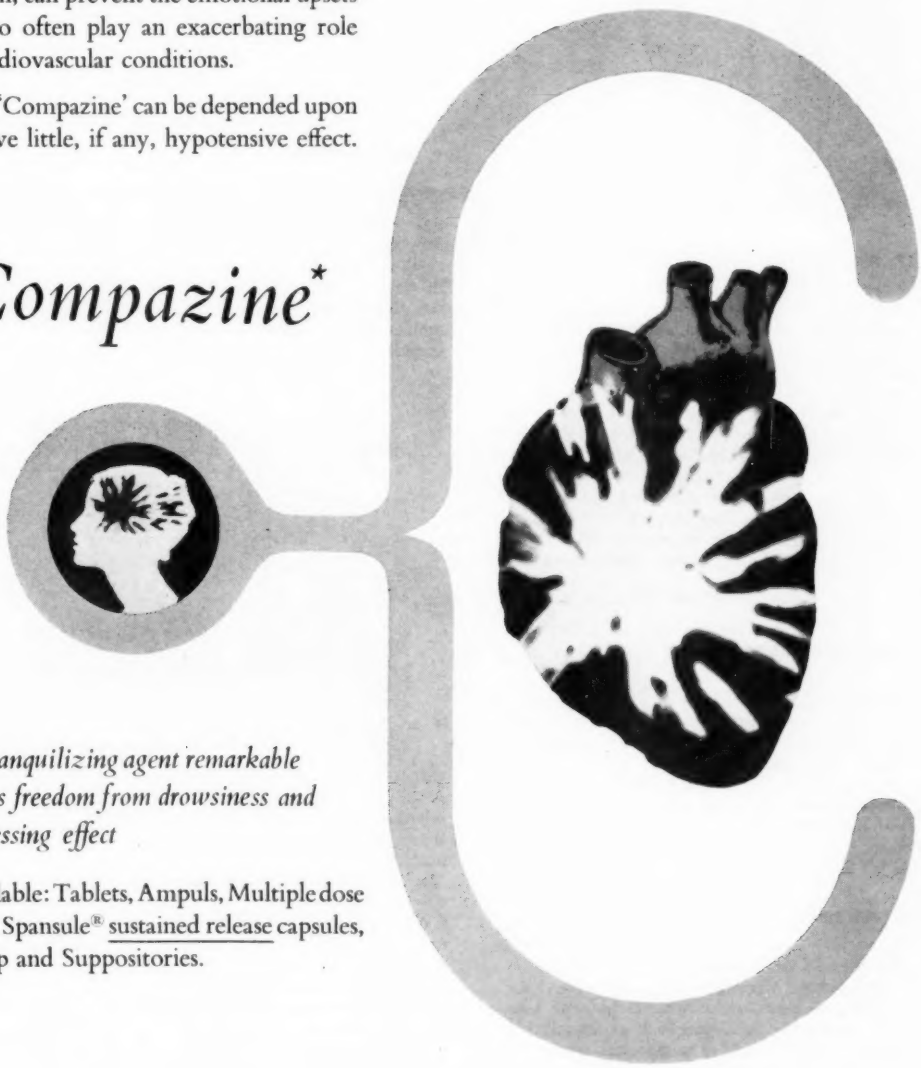
INDICATIONS FOR USE: Head colds, bronchitis, inflammation of the pharynx and trachea, laryngitis, and asthma.
DOSAGE AND ADMINISTRATION: Children less than four years of age, ½ teaspoonful (2.5 cc.) one to four times daily; older children, 1 to 2 teaspoonfuls (5 to 10 cc.) one to four times daily.
HOW SUPPLIED: 1 pt. bottles.
PRODUCER: Wyeth Laboratories, Philadelphia 1.

(Continued on page A-134)

To prevent emotional upsets in cardiovascular conditions

'Compazine', by controlling anxiety and tension, can prevent the emotional upsets that so often play an exacerbating role in cardiovascular conditions.

And, 'Compazine' can be depended upon to have little, if any, hypotensive effect.



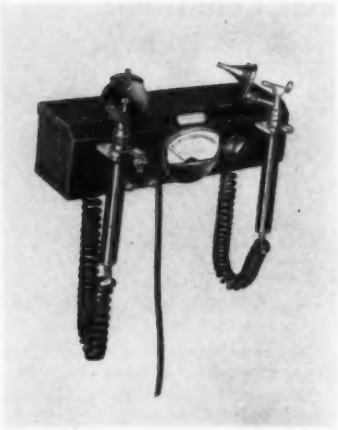
*Compazine**

the tranquilizing agent remarkable for its freedom from drowsiness and depressing effect

Available: Tablets, Ampuls, Multiple dose vials, Spansule® sustained release capsules, Syrup and Suppositories.

Smith Kline & French Laboratories, Philadelphia

★T.M. Reg. U.S. Pat. Off. for prochlorperazine, S.K.F.



• WALL TRANSFORMER

DESCRIPTION: An office power source for Welch Allyn diagnostic instruments, the unit is designed for permanent mounting on office or hospital wall and connects to regular 110 or 220 V electric circuits. The transformer provides lightweight handles, each with an 8 ft. coiled cord, for two instruments. Instruments are lighted or turned off automatically when handles are lifted or returned to the supports. Binding posts are provided for connecting instruments with cord tips. The unit also includes a sensitive rheostat to control voltage and an easily read voltmeter.
PRODUCER: Welch Allyn, Inc., Skaneateles Falls, N.Y.

• STERILE BLADE PACKAGE

DESCRIPTION: A sterile B-P® Rib-Back blade of carbon steel is heat-sealed in a moisture proof and puncture-resistant envelope that can be autoclaved. The blade may be attached to the knife handle while in the opened package.
HOW SUPPLIED: All sizes in 1 gross boxes.
PRODUCER: Bard-Parker Company, Inc., Danbury, Conn.

• VESPRIN®

PURPOSE: To treat psychotic conditions.
COMPOSITION: A phenothiazine derivative.
INDICATIONS FOR USE: Schizophrenic and manic states and other psychoses such as organic brain disease, and the alcohol withdrawal syndrome.
CAUTION: Photosensitivity has been observed infrequently and hyperthermia rarely.
HOW SUPPLIED: 10, 25 and 50 mg. tablets in bottles of 50 and 500, and 1 cc. (20 mg.) ampules.
PRODUCER: E. R. Squibb & Sons, division of Olin Mathieson Chemical Corp., New York.

• URISTIX REAGENT STRIPS

PURPOSE: To test for proteinuria and glycosuria.
DESCRIPTION: This "dip and read" test is done with a firm paper strip, the end of which is impregnated with reagents that change color with positive tests. The operator dips the strip in the specimen and compares the result with the color guide printed on the bottle label. The test portion for proteinuria is separated by a barrier from the test for glycosuria so that color changes are easily read.
HOW SUPPLIED: Bottles of 125 reagent strips.
PRODUCER: Ames Company, Inc., Elkhart, Ind.

• CHART DIVIDERS

DESCRIPTION: These dividers are used for tabbing and indexing the charts of the various admissions of a patient so that the record of each admission may be identified at a glance. Arranged so that the most recent admission is always at the front, the dividers are suitable for use with either the unit or the serial-unit system of numbering.
PRODUCER: Physicians' Record Company, Chicago.

• DOUBLE-BEAM IR-5 SPECTROPHOTOMETER

DESCRIPTION: This simplified infraray instrument contains an automatic flat-bed recorder which permits use of preprinted, file-size charts; the spectrum is visible at all times. Notations may be made on the chart while a scan is in progress. Manual scans can be made when the wavelength drive motor is stopped. Fast qualitative and quantitative scanning is possible with wavelength accuracy of 0.02 μ and resolution as high as 0.03 μ at 10 μ. The instrument is suited for differential analysis and automatically compares two samples or one sample and reference. It can also operate as a single-beam instrument. It records linearly in transmittance and wavelength and will scan the entire 2 to 16 μ range in 16 minutes. Features which simplify use include five fixed controls, push-button operation and automatic recording.
PRODUCER: Beckman Scientific Instruments Division, Fullerton, Calif.

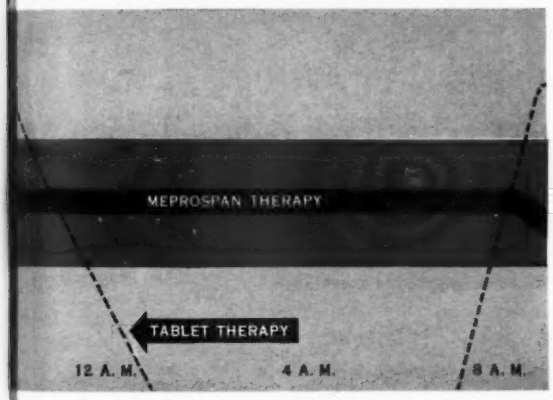
(Continued on page A-138)

Meprospan*

*TRADE-MARK

MEPROBAMATE IN PROLONGED RELEASE CAPSULES

muscle 'round the clock



OSPAN CAPSULES AT BEDTIME
NINTERRUPTED SLEEP THROUGH-
IGHT.

Each Meprospan capsule contains 200 mg. of meprobamate in the form of coated pellets. The drug is continuously released over a period of 10 to 12 hours...

- maintains constant level of relaxation
- minimizes the possibility of side effects
- simplifies patient's dosage schedule

Dosage: Two Meprospan capsules q. 12 h. **Supplied:** Bottles of 30 capsules.

Each capsule contains: Meprobamate (Wallace) . . . 200 mg.
2-methyl-2-n-propyl-1,3-propanediol dicarbamate

Literature and samples on request

WALLACE LABORATORIES, *New Brunswick, N. J.*

CME6565-38

• ARM BOARD

DESCRIPTION: Made to fit all operating tables, the unit attaches to the table under the mattress. Two arm trays are incorporated into one unit for parallel position on one side of the table or for extension to both sides. Both trays are covered with conductive rubber over foam rubber pads and are fully adjustable. The upper tray rotates 360 degrees in a horizontal plane and swivels 60 degrees upward and 80 degrees downward from the horizontal on a 6 in. arm around a 20 in. long stanchion graduated in 1¼ in. increments. A spring-loaded mechanism provides positive locking. The lower tray rotates through 340 degrees on its stanchion and adjusts on its 4 in. rod. The lightweight unit can be quickly attached and repositioned.
PRODUCER: Sierra Engineering Co., Sierra Madre, Calif.

• L-GLUTAVITE® WITH ANDROGEN-ESTROGEN

PURPOSE: To provide a somatic and cerebral tonic for middle-aged and aging patients.
COMPOSITION: Each 6 tablets provide:

Monosodium l-glutamate	3.5 gm.
Methyltestosterone	2.5 mg.
Ethinyl estradiol	0.005 mg.
Niacin	45 mg.
Pyridoxine hydrochloride	1 mg.
Thiamine mononitrate	1 mg.
Riboflavin	2 mg.
Ascorbic acid (as calcium ascorbate)	30 mg.
Ferrous sulfate (exsiccated)	32 mg.

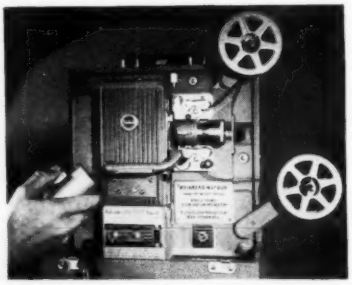
DOSAGE AND ADMINISTRATION: 2 tablets three times daily, or as directed.
HOW SUPPLIED: Bottles of 100.
PRODUCER: Gray Pharmaceutical Co., Inc., Newton, Mass.

• POWERPAK 582

DESCRIPTION: Used to provide power for general room illumination in the event of power failure during surgery, this unit is equipped with a dual voltage supply which permits carrying a mixed 12 or 18 V load, or both, in any combination that does not exceed a total load of 250 W. It is interlocked with the major operating light and general lighting fixture in such a manner that the emergency circuit will not function unless the standard circuit was in operation prior to power failure. Two charging circuits are provided: One, a constant-trickle charge, operates as long as the alternating current is on; the other, a manually operated high-rate charger, can be used to recharge the batteries rapidly. Automatic protection is provided to prevent battery overcharge.
PRODUCER: Wilmot Castle Co., Rochester, N.Y.

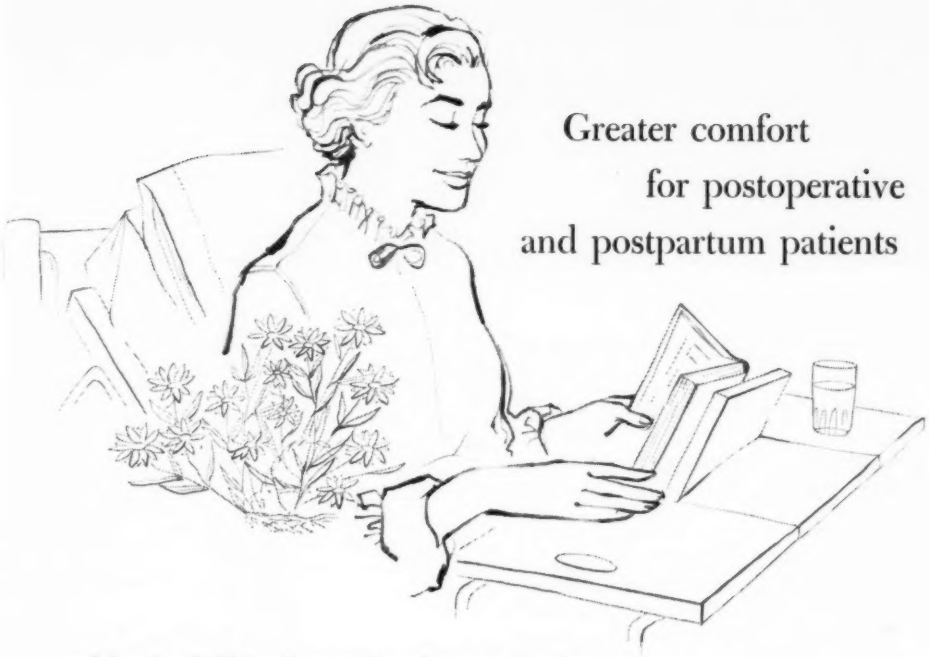
• LOWILA® EMOLLIENT

PURPOSE: To treat excessively dry, scaly skin.
COMPOSITION: KEROHYDRIC® (a dewaxed oil-soluble, keratin-moisturizing fraction of lanolin) in an acid-buffered polyethylene glycol monostearate emulsion.
DESCRIPTION: When applied to the skin, this lotion provides a partially occlusive breathing film that supplies its own water to the dehydrated keratin layer, prevents excessive evaporation when the atmosphere is dry, and allows the skin to absorb water from an atmosphere with normal humidity. It also supplements natural skin oils, restoring the protective action of skin lipids.
PRODUCER: Westwood Pharmaceuticals, Buffalo.



• KODAK ANALYST II PROJECTOR
With Weinberg-Watson Modification

DESCRIPTION: Any length of 16 mm. film up to 400 ft. can be projected on this machine which features variable projection speeds from 6 to 20 frames per second, instant single-frame viewing by remote-control push button, reverse motion at any moment desired, and flickerless projection. Excellent viewing is assured by an EKTANON® 1:6 lens of 2 in. focal length and by 750 W light power. No refocusing is required for single framing, and a built-in cooling system prevents film overheating and buckling at slow speeds. A mirror and screen, which are part of the unit, make table-top viewing possible. Designed for the radiologist doing cineradiography, the unit is suitable for any time-motion study. The projector weighs less than 35 lb. and is built into its carrying case.
PRODUCER: Eastman Kodak Company, Rochester, N.Y.



Greater comfort for postoperative and postpartum patients

abdominal distention and urinary retention
can often be prevented or promptly relieved
– with less need for uncomfortable enemas and catheters

Urecholine®

Chloride
(Bethanechol Chloride)

'Urecholine' helps restore normal function after surgery and childbirth by increasing the muscular tone of the gastrointestinal and urinary tracts. Postoperative "gas" pains can frequently be prevented or promptly relieved—with less need for uncomfortable enemas, intubation, and suction apparatus. Micturition is facilitated—without the discomfort and risk of infection inherent in catheterization.

Administration and dosage: may be given prophylactically or therapeutically after surgery or childbirth. Usual oral dosage: 10 to 30 mg. three or four times daily. Usual subcutaneous dosage: 5 mg. three or four times daily.

Other indications: gastric atony and retention following vagotomy and other surgical procedures; chronic functional urinary retention due to atony without obstruction; megacolon, including congenital megacolon (Hirschsprung's disease); certain cases of paralytic ileus; to counteract side effects of antihypertensive ganglionic blocking drugs.

Supplied: 5 mg. and 10 mg. tablets, bottles of 100; 1-cc. ampuls containing 5 mg.

Urecholine is a trade-mark of MERCK & CO., INC.

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THE MEDICAL Bookman

► A TEXT-BOOK OF X-RAY DIAGNOSIS

By British authors, in four volumes. Edited by S. Cochrane Shanks, M.D., Director, X-ray Diagnostic Department, University College Hospital, and Peter Kerley, M.D., Director, X-ray Department, Westminster Hospital, London, England. Ed. 3, Vol. 1. 521 pages with 533 illustrations. 1957, W. B. Saunders Company, Philadelphia and London. $18.00.

The material of many British authorities has been assembled and edited, as in past editions, to present the reader with a comprehensive knowledge of the roentgenographic technics, clinical and pathologic findings, and the associated roentgenographic findings of each entity discussed, and also to incorporate the many advances in radiology. Emphasis has been placed on the fundamental principles in interpretation with regard to daily clinical problems encountered in an average x-ray department.

This volume has the same five divisions as its earlier counterpart, i.e., central nervous system, the teeth and jaws, the eye, the accessory nasal sinuses and the ear and temporal bone. Almost 100 illustrations have been added, and the old plates have been printed with much more clarity than previously, so that the detail therein is more readily appreciated.

The sections on angiography, intracranial lesions and the spinal cord have been expanded more than the others. The additional discussions, particularly in cerebral angiography, contribute to the value of the book. This is one of the few medically edited texts in which such a comprehensive discussion is devoted to the roentgenographic manifestations of diseases of the teeth and jaw.

Although the differences between this edition and the second edition are not radical, they nevertheless are important.

S. B. F.

► PRE-EMPLOYMENT DISABILITY EVALUATION

By William A. Kellogg, M.D., formerly associated with the Medical Department, Douglas Aircraft Company, Inc., Long Beach, California, and Clinical Professor of Surgery, New York Polyclinic Post-Graduate Medical School, New York. 155 pages. 1957, Charles C Thomas, Springfield, Illinois. $10.50.

Published as a loose-leaf notebook, this excellent reference manual gives a brief but encompassing description of the various disabilities, diseases and conditions encountered in pre-employment examinations. The various systems of the body are discussed, including a section on nutritional and constitutional diseases and conditions. The relationship of these disabilities to the individual's working capacity must be determined by the examining physician so that prospective employees can be assigned to jobs within their physical capacities. I recommend this manual to all physicians in the pre-employment examination field, and to those physicians doing routine examinations in industry.

I. P. F.

(Continued on page A-148)

for the best in
tetracycline therapy...
new, rapidly effective

COSA-TETRACYN

1. highest, fastest tetracycline blood levels Analysis of a 4-way crossover study confirms that Cosa-Tetracyn produces the highest, fastest blood levels of all available tetracycline enhancement formulations.[1]

2. greatest consistency of high tetracycline blood levels
In a 4-way crossover study, Cosa-Tetracyn demonstrated greatest consistency of high blood levels compared to tetracycline-citric acid, tetracycline phosphate complex, and tetracycline-sodium hexametaphosphate.[1]

3. safe, physiologic advantages of glucosamine Completely safe as an enhancement agent, glucosamine is nontoxic, sodium free, nonirritating to the gastrointestinal tract, and there is evidence it may influence favorably the bacterial flora of the intestine.

The most widely prescribed broad-spectrum antibiotic now potentiated with glucosamine, the enhancing agent of choice.

Cosa-Tetracyn is supplied in capsules, 250 mg., bottles of 16 and 100; and half-strength capsules (125 mg.) for long-term therapy or pediatric use, bottles of 25 and 100.

1. Carlozzi, M.: Antibiotic Med. & Clin. Therapy 5:146 (Feb.) 1958.

Pfizer Laboratories
Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.

AMINE-POTENTIATED TETRACYCLINE

COSA-TETRACYN

► TUMOR SURGERY OF THE HEAD AND NECK

By Robert S. Pollack, M.D., Clinical Instructor in Surgery, Stanford University School of Medicine, San Francisco. 101 pages with 49 figures. 1957, Lea & Febiger, Philadelphia. $5.00.

Tumor surgery constitutes one of the major problems in diseases involving the head and neck. This textbook covers diagnosis, diagnostic methods, indications for irradiation therapy, operative management, and management of recurrent cancer.

The section on operative technic describes the following procedures in detail: surgery for cancer of the lower lip; hemimandibular resection; combined operation for cancer of the tongue and floor of the mouth; division of the mandible for better approach to cancer within the lower part of the mouth, followed by reanastomosis of the mandible; a modified approach to intra-oral cancer in which the mandible is not disturbed; and operations for cancer of the gum, palate and the maxillary and other paranasal sinuses. Management of tumors of the submaxillary, parotid and thyroid glands and of lesions of the larynx and cervical lymph nodes is well described.

The author states that management of recurrent cancer in the head and neck should be as aggressive and energetic as that of the primary lesion, because some patients still may be cured and numerous patients in whom the cancer is incurable need therapy for relief of pain, hemorrhage or obstruction. In his opinion, recurrent cancer generally is best treated by x-ray or radium therapy.

This text is intended primarily for surgeons, and although nothing new is presented, the concise description of a single regional surgical problem is of value.

Y. S.

► MODERN PERINATAL CARE

By Leslie V. Dill, M.D., Associate Clinical Professor, Obstetrics and Gynecology, Georgetown University School of Medicine, Washington, D.C. 309 pages. 1957, Appleton-Century-Crofts, Inc., New York City. $6.50.

A general summary of current thought on the care of the woman during the antepartum and postpartum periods is the basis of this text. Obstetric problems discussed include nutrition, abortion, pelvic mensuration, and toxemia and anemias of pregnancy, as well as such complications in pregnancy as heart disease, diabetes mellitus, thyroid disorders, tuberculosis and venereal diseases. Problems relative to the infant also are considered in brief discussions of fetal mortality, birth injuries, congenital malformations and infant feeding. The general obligations and regulations imposed on the obstetrician by the law are reviewed. The final chapter presents a good summary of the tenets of the Roman Catholic Church as they pertain to obstetrics. This book should be of most value to those in general practice.

L. A. A.

► INTRODUCTION TO CLINICAL ENDOCRINOLOGY

By A. Stuart Mason, M.D., Senior Lecturer, Medical Unit, The London Hospital, London, England. 192 pages. 1957, Charles C Thomas, Springfield, Illinois. $4.50.

Excellent descriptions of the more common endocrine abnormalities are presented in chapters on the hypothalamus and posterior pituitary, anterior pituitary, thyroid, adrenals, parathyroids, spontaneous hypoglycemia, gonads, testis, ovary and breast. The introductory chapter gives general principles and the appendix deals with the laboratory investigation of endocrine dysfunction.

Since the author deliberately omitted presentation of alternate views and all references to the literature, the book tends to be didactic in places. The brevity of the text has allowed only scant mention of some of the less common, though important, syndromes such as toxic nodular goiter and Klinefelter's syndrome. Also, as stated in the preface, the author has devoted a large portion of the text to various endocrinopathies in the light of applied physiology. Accordingly, the sections on the use of laboratory aids in diagnosis and those on treatment suffer from brevity. Despite these shortcomings, the book is an excellent introduction to endocrine disorders and can be read with profit by those who wish a steppingstone to the more comprehensive texts in the complicated field of endocrinology.

R. V. R.

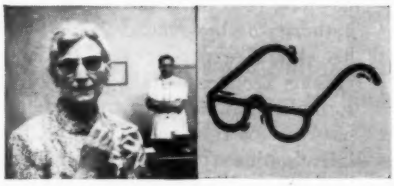
(Continued on page A-150)

in each of these indications for a tranquilizer...

SR is a cardiac patient. His doctor put him on ATARAX because (+) it is an anti-arrhythmic and non-hypotensive tranquilizer.

Other tranquilizers added to PN's g. i. discomfort (he has ulcers). But now his doctor has him on ATARAX because (+) it lowers gastric secretion while it tranquilizes.

Asthmatic JL used to have frequent tantrums followed by acute bronchospasm. Her family doctor tranquilized her with ATARAX because (+) it is safe, even for children.



Senile anxiety and persecution complex dogged Mrs. K. until her doctor prescribed ATARAX Syrup. (+) It tastes good, and it's a perfect vehicle for Mrs. K's tonic.

Dosage: Children, 1-2 *10 mg.* tablets or 1-2 tsp. Syrup t.i.d. Adults, one *25 mg.* tablet or 1 tbsp. Syrup q.i.d.

Supplied: 10, 25 and 100 mg. tablets, bottles of 100. Syrup, pint bottles. Parenteral Solution, 10 cc. multiple-dose vials.

...ATARAX gives you an extra benefit

(HYDROXYZINE)

Roerig Rx

New York 17, New York
Division, Chas. Pfizer & Co., Inc.

► DRUGS; THEIR NATURE, ACTION AND USE

By Harry Beckman, M.D., Director, Department of Pharmacology, Marquette University Schools of Medicine and Dentistry, Milwaukee. 728 pages with 126 illustrations. 1958, W. B. Saunders Company, Philadelphia and London. $15.00.

Designed for the undergraduate medical student, this is a well-organized textbook with which to supplement laboratory, lecture and conference-room studies. There are three sections: The first presents an orientation of pharmacology among the other preclinical studies; the second gives a description of the broad background of the science and an exposition of the bases from which advances are made, and the third and major portion of the text gives a discussion of the actions and uses of drugs.

The arrangement, type and double-column page make this text very easy to read. While this book serves its purpose for the particular group of students for whom it was written, I feel that the practicing physician and intern will refer to more complete volumes for the pharmacology, etc. of many of the drugs that are mentioned.

I. P. F.

► THE LOWER URINARY TRACT IN CHILDHOOD; Some Correlated Clinical and Roentgenologic Observations

By Sven Roland Kjellberg, Nils Olof Ericsson and Ulf Rudhe, Stockholm, Sweden. 298 pages with 265 illustrations. 1957, The Year Book Publishers, Inc., Chicago. $18.00.

It is not often that a book can be described as truly new and different in its entirety; such a statement can, however, be made about this volume. It is not only a new approach to this vast problem, but also a unique and valuable approach to the diagnostic field, which makes definitive therapy possible.

With the authors' technic for biplane roentgenographic studies in micturition cystourethrography, using a nonirritating contrast medium, the many causes for lower urinary tract problems can be separated and identified. For the most part, this cannot be accomplished with the conventional retrograde-type studies employed in American clinics.

A masterful description of embryology, anatomy, physiology and technic is given in the first three chapters. The material for the subsequent chapters was collected at the Pediatric Clinic of Karolinska Sjukhuset, Stockholm, between 1952 and 1956, and contains expert descriptions of the clinical, roentgenographic, endoscopic and therapeutic aspects of the following conditions: ectopic ureter and ureterocele, neurogenic bladder, bladder neck obstruction, selected aspects of urinary tract infection, urethral valves, stricture of the urethra, urethral polyp, congenital hypertrophy of the verumontanum, intersexuality, diverticula of the urethra, and enuresis. In particular, the chapters on ectopic ureter, ureterocele, bladder neck obstruction and urethral valves deserve careful attention and application by us in this country.

This book is more than recommended reading; it is necessary reading for radiologists and urologists who have specific pediatric interests and contacts.

S. B. F.

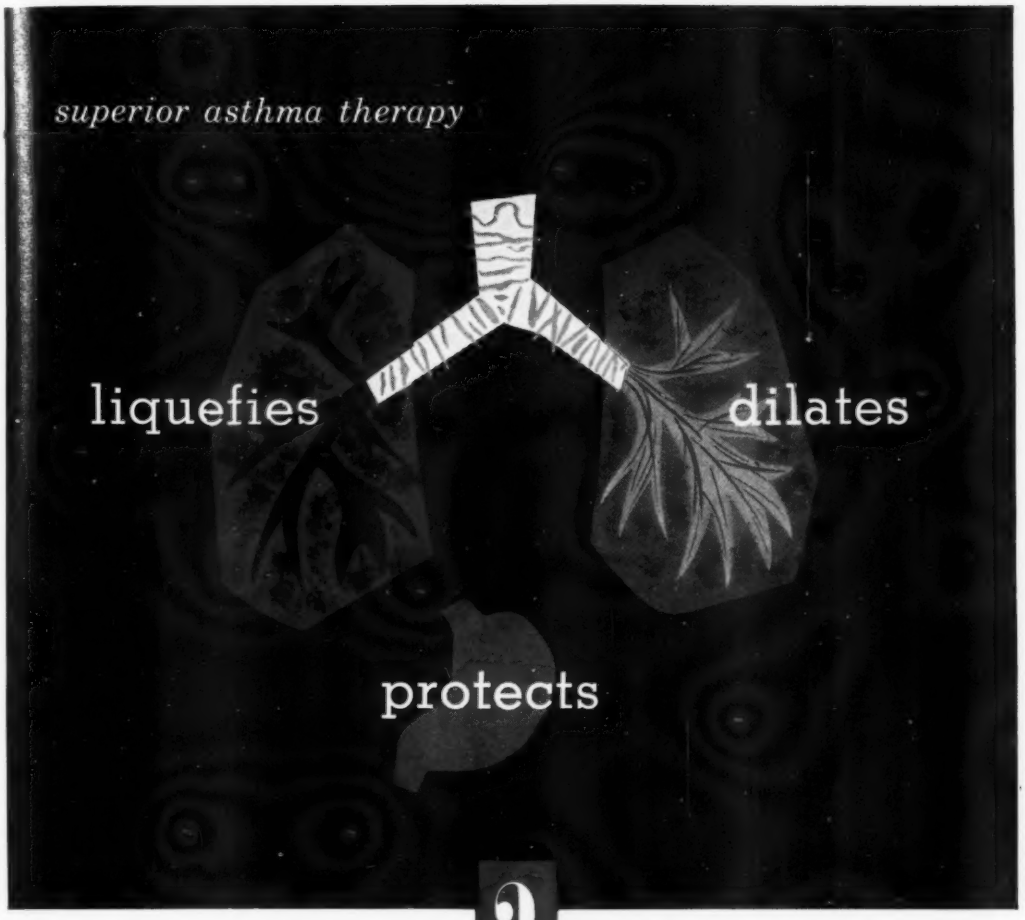
► BONE DISEASES IN MEDICAL PRACTICE

By I. Snapper, M.D., Director of Medicine and Medical Education, Beth-El Hospital, Brooklyn, and formerly Professor of Medicine, Medical School of the University of Amsterdam, Amsterdam, Holland. 229 pages, illustrated. 1957, Grune & Stratton, Inc., New York and London. $15.00.

Occasionally a book is published which looms as an eminent contribution to medical knowledge. Such is this volume, written by an author who has long been duly recognized as an outstanding authority on bone metabolism and disease. From his clinical experiences in Holland, China and various sections of the United States, he has formulated an excellent treatise on a subject that has received relatively little attention until recent investigations propounded its importance. The book generally reflects his intense interest in all facets of bone disorders, especially those characterized by faulty metabolism and obscure clinical symptomatology. Great interest now is being stimulated by information obtained in the clinical laboratory from the use of radioisotopes. The realization by the majority of the medical profession that bone diseases are becoming more read-

(Continued on page A-152)

superior asthma therapy



Dainite®-KI provides 3 essential actions for superior asthma therapy

. . . in a single, inclusive antiasthmatic tablet. Slow release of coated KI prevents "dumping" and promotes long-lasting *liquefaction* of sticky, mucous plugs. *Un*coated aminophylline assures high theophylline blood levels for greater protection and extra bronchial *dilatation*. *Protective* factors guard against gastric irritation usually caused by therapeutic oral doses of aminophylline.

each Dainite-KI tablet contains:

Potassium iodide	5 gr.
Aminophylline	3 gr.
Ephedrine HCl	¼ gr.
Phenobarbital	¼ gr.
Ethyl aminobenzoate	¼ gr.
Aluminum hydroxide	2½ gr.

Dainite®-KI

comprehensive protection for the asthmatic

Neisler *Irwin, Neisler & Co. • Decatur, Illinois*

ily evident, and therefore more expertly treated. instills a rational approach toward a proper therapeutic background. Further, it initiates a definite need for better understanding of differential diagnostic patterns.

Beginning with a chapter on bone physiology, this monograph includes a comprehensive review of bone disease. However, its shortcomings, although few, seemingly are magnified by a failure to summarize some chapters and, to some extent, by the brief references to clinical therapy. Nonetheless, it is truly representative and will be used widely by all practitioners, specialists and those with ancillary medical backgrounds who are interested in bone diseases. Based on a subject that needs clarification, this volume will most likely be accepted as a cornerstone in its field.

E. H. O'P.

► A TEXTBOOK OF CLINICAL NEUROLOGY With an Introduction to the History of Neurology

By Israel S. Wechsler, M.D., Consulting Neurologist, The Mount Sinai Hospital, New York. Ed. 8. 782 pages with 179 illustrations. 1958, W. B. Saunders Company, Philadelphia and London. $11.00.

The text is divided into five sections. The first is devoted to methods of examination. This proceeds along traditional lines with a discussion of reflexes, sensory examination, and examination of the cranial nerves. Brief subdivisions deal with special tests such as electromyography and examination of the spinal fluid. A special chapter on psychologic diagnosis has been written by David Wechsler.

The next three sections deal with diseases involving the spinal cord, including the dystrophies and myasthenia gravis, which, strictly speaking, are diseases of the peripheral musculature; the peripheral nerves, with discussion based on anatomic divisions; and diseases of the brain, including a discussion of general symptomatology and signs of focal brain disease. The customary division by etiologic categories, such as circulatory disturbances of the brain, encephalitis and tumors of the brain, is employed. In the concluding section of the book, neuroses are discussed. Although such a chapter occurs with declining frequency in neurologic texts, the author states in the preface his reasons for including it.

The field of neurology is a rapidly expanding one in which many traditional ideas currently are being intensively investigated and revised. The progressive increase in size of each edition of this book is indicative of the growing complexity of the field. To remain abreast of the advances of neurologic knowledge in all its areas is a formidable task for any author, but the continued existence of this volume over 30 years is a tribute to its writer's success in this regard. This book should provide a good introduction to the subject of neurology for medical students and nonspecialists.

D. D.

► CLINICAL ASPECTS OF ARTERIOSCLEROSIS

By Seymour H. Rinzler, M.D., Associate Physician, Beth Israel Hospital, New York. 339 pages, illustrated. 1957, Charles C Thomas, Springfield, Illinois. $8.75.

Emphasis is placed on the problem of arteriosclerosis as the physician sees it. The author covers the cardiac aspects of arteriosclerosis in minute detail, discussing such items as coronary circulation, the natural history of coronary disease, tests for heart disease, the prognosis of angina pectoris, and the differential diagnosis and management of patients with arteriosclerosis. The various surgical indications and the details of medical management are outlined. Consideration is given to such phases as low salt diets, cardiac medications, management of arrhythmias, and the treatment of acute myocardial infarction. The sections are well illustrated with electrocardiogram reproductions, diagrams and tables.

Proceeding to a discussion of the cerebral aspects of arteriosclerosis, the author considers cerebral circulation and describes in detail the diagnostic procedures and treatment. The last portion of the book covers arteriosclerosis of the aorta and peripheral vessels and the retinal, renal and pulmonary aspects of this disease.

Throughout this work, the author discusses primarily the pathologic changes caused by arteriosclerosis. So far as etiology and prevention are concerned, he presents only the major schools of thought, and has summarized the various antiarteriosclerotic agents in more or less chronologic fashion.

Y. S.

(Continued on page A-154)

COMPREHENSIVE CONTROL OF CONSTIPATION

PROVIDES SOFT STOOLS GENTLY STIMULATED TO EVACUATION

DOXINATE® with DANTHRON (Doxan)

— the original dioctyl sodium sulfosuccinate fecal softener combined with danthron, the non-irritating, non-habit forming laxative —

Comprehensive control of constipation with Doxan . . .

★ prevents fecal dehydration and gently stimulates the lower colon in functional constipation

★ synergistically provides, with a subclinical dosage, peristaltic action on a soft, "normal" intestinal content rather than on the hardened mass typical of constipation

★ results in soft stools gently stimulated to evacuation . . . and restores normal bowel habits

Doxinate with Danthron (Doxan) is supplied as brown, capsule-shaped tablets containing 60 mg. dioctyl sodium sulfosuccinate and 50 mg. 1,8-dihydroxyanthraquinone.

Usual adult dose: One or two capsule tablets at bedtime. Bottles of 30 and 100.

When fecal softening alone is indicated— Doxinate 240 mg.—provides optimal once-a-day dosage for maintenance therapy.

Doxinate is a registered trademark of Lloyd Brothers, Inc.

LLOYD BROTHERS, INC.
CINCINNATI 3, OHIO

► CLINICAL AND IMMUNOLOGIC ASPECTS OF FUNGOUS DISEASES

By J. Walter Wilson, M.D., Clinical Professor of Medicine, University of Southern California, Los Angeles. American Lecture Series. 280 pages. 1957, Charles C Thomas, Springfield, Illinois. $6.75.

This treatise comes at a time when those who fight the more common bacterial diseases seem to be victorious in their efforts, owing to the number, variety and curative properties of the antibiotics which are now available. However, one's security in dealing with diseases caused by viruses and fungi still depends on a very few curative agents.

The author has done an excellent job in presenting the up-to-date clinical and immunologic material related to coccidioidomycosis, sporotrichosis, North and South American blastomycosis, histoplasmosis, actinomycosis and the various manifestations of dermatophytosis. His 20 years' experience in studying the course of coccidioidomycosis in California has given him an insight into the immunology of this disease and the value of skin tests, complement fixation, etc. In addition, he shares with the reader his knowledge of other fungous diseases, gleaned through his association with most of the leaders in these fields.

His therapeutic approach to fungous disease is up to date but conservative. In those fungous diseases in which an adequate amount of skin-test material has been studied, the hypersensitivity revealed by the intracutaneous reaction of the delayed tuberculin type seemed to be related to the patient's ability to resist the progress of the disease immunologically. On this basis, he feels artificial desensitization would be illogical and perhaps dangerous.

This handbook should be read by all those interested in general medicine, as well as by dermatologists and mycologists.

J. H. L.

Books received are acknowledged in this department. As space permits, books of principal interest to our readers are reviewed more extensively.

Clinical Heart Disease. By Samuel A. Levine, M.D., Clinical Professor of Medicine, Harvard Medical School, Boston. Ed. 5. 673 pages with 216 illustrations. 1958, W. B. Saunders Company, Philadelphia and London. $9.50.

De Motu Cordis; Movement of the Heart and Blood in Animals. An anatomic essay by William Harvey in the original Latin, translated by Kenneth J. Franklin. 209 pages. 1957, Charles C Thomas, Springfield, Illinois. $3.50.

An Introduction to Medical Mycology. By George M. Lewis, M.D., Professor of Clinical Medicine, Mary E. Hopper, M.S., Research Fellow in Medicine, Cornell University Medical College, New York, J. Walter Wilson, M.D., Clinical Professor of Medicine, University of Southern California, and Orda A. Plunkett, Ph.D., Professor of Botany, University of California, Los Angeles. Ed. 4. 453 pages with 118 illustrations. 1957, The Year Book Publishers, Inc., Chicago. $15.00.

General Pathology. Based on lectures delivered at the Sir William Dunn School of Pathology. Edited by Sir Howard Florey, Professor of Pathology, Sir William Dunn School of Pathology, University of Oxford, Oxford, England. Ed. 2. 932 pages, illustrated. 1958, W. B. Saunders Company, Philadelphia and London. $16.00.

Your Child Is What He Eats. A common sense guide to child feeding from birth to adolescence. By Harold D. Lynch, M.D., Fellow, American Academy of Pediatrics, Evansville, Indiana. 188 pages, illustrated. 1958, Henry Regnery Company, Chicago. $3.75.

Selected Writings of Walter E. Dandy. Compiled by Charles E. Troland, M.D. and Frank J. Otenasek, M.D. 789 pages, illustrated. 1957, Charles C Thomas, Springfield, Illinois. $15.00.

The Respiratory Muscles and the Mechanics of Breathing. By E. J. Moran Campbell, M.D., Assistant, Department of Medicine, Middlesex Hospital, London, England. 131 pages with 32 illustrations. 1958, The Year Book Publishers, Inc., Chicago. $4.25.

Foundations of Neuropsychiatry. By Stanley Cobb, M.D., Bullard Professor Emeritus of Neuropathy, Harvard Medical School, Boston. Ed. 6. 313 pages, illustrated. 1958, The Williams & Wilkins Company, Baltimore. $5.00.

The Chemistry of Blood Coagulation. American Lecture Series. By Paul Morawitz, Marburg, Germany. Translated by Robert C. Hartmann, M.D. and Paul F. Guenther, Ph.D., Departments of Medicine and German, Vanderbilt University, Nashville. 194 pages. 1958, Charles C Thomas, Springfield, Illinois. $4.50.

Preventive Medicine for the Doctor in his Community; an Epidemiologic Approach. By Hugh Rodman Leavell, M.D., Professor of Public Health Practice, Harvard School of Public Health, Boston, and E. Gurney Clark, M.D., Professor of Epidemiology, School of Public Health and Administrative Medicine of the Faculty of Medicine, Columbia University, New York, with 19 contributors. Ed. 2. 689 pages, illustrated. 1958, The Blakiston Division, McGraw-Hill Book Company, Inc., New York. $10.00.

Current Therapy 1958; Latest Approved Methods of Treatment for the Practicing Physician. Edited by Howard F. Conn, M.D., Uniontown, Pennsylvania, with 12 consulting editors. 827 pages. 1958, W. B. Saunders Company, Philadelphia and London. $12.00.

SPECIFIC FOR PAINFUL MUSCLE SPASM

PARAFLEX*

Chlorzoxazone†

skeletal muscle relaxant

HIGHLY EFFECTIVE WITH PRACTICAL DOSAGE

in common traumatic, orthopedic, arthritic and rheumatic disorders, including: low back pain • sprains • strains • rheumatoid arthritis • osteoarthritis • spondylitis • myalgia • fibrositis • cervical root syndrome • wry neck • disc syndrome

EFFECTIVELY RELIEVES SPASM AND PAIN—In a controlled, double-blind study, marked improvement was reported in all but one of 15 patients treated with PARAFLEX.[1] Another investigator noted that symptoms were at least partially alleviated in all of the patients treated.[2]

PRODUCES LONG-LASTING BENEFITS—Significant blood levels following the administration of PARAFLEX are maintained for periods of 6 hours or more.[3] In most patients, the beneficial effects of PARAFLEX persisted for approximately six hours.[4]

AVERAGE DOSE—SIX TABLETS DAILY—With PARAFLEX, just one or two tablets, three times daily is an average effective dose. In experimental studies, PARAFLEX was found to be from one and one-half to three times as potent as other commonly used muscle relaxants.

IS WELL TOLERATED—Side effects are uncommon and seldom severe enough to require discontinuation of the drug.[5] Other clinicians have encountered few side effects to date.[1,2,4,6,7]

SUPPLIED—Tablets, scored, orange, bottles of 50. Each tablet contains 250 mg. of PARAFLEX.

REFERENCES—(1) Settel, E.: Personal communication. (2) Holley, H. L.: Personal communication. (3) Burns, J. J.; Trousof, N., and Brodie, B. B.: To be published. (4) Smith, R. T.: To be published. (5) Peak, W. P., and Smith, R. T.: To be published. (6) Wiesel, L. L.: Personal communication. (7) Passarelli, W. W.: Personal communication.

CLINICAL RESULTS WITH PARAFLEX

Investigator	Disorder	Number of patients treated	Number of patients benefited	Comment
Settel[1]	acute low back pain, acute traumatic myofascitis, or osteoarthritis	15	14	response excellent in nine, good in five
Holley[2]	wry neck, cervical spondylitis, and disc syndrome	10	10	improvement, ranging from some amelioration of symptoms to profound relief
Wiesel[6]	advanced osteoarthritis	12	10	less muscle spasm and pain
Passarelli[7]	degenerative and rheumatoid arthritis	9	9	improvement, with less stiffness and freer motion
Passarelli[7]	varied arthritic rheumatic, and traumatic disorders	6	6	less stiffness, less pain
Totals		52	49	

*Trade-mark †U. S. Patent Pending

174A88

The Medical Muse

RICHARD ARMOUR

WHERE'S THE DOCTOR?

Is there a doctor in the house?
If you should ask a doctor's spouse,
The chances are, statistics show,
The answer you would get is, "No."

The doctor's at the office, working
(It's after hours and rather irking),
Or in the lab or at the clinic
Or answering some phoning cynic,

Or on a call out in the sticks
Or at a meeting, just for kicks,
Or north of Rio, south of Nome,
But not, or very rarely, home.

ODE TO A CLINICAL THERMOMETER

Oh, precious little instrument
Of mercury and glassware blent,
With black gradations, straight and formal,
With arrow indicating normal,
And, over ninety-eight point six,
Red lines (the patient's in a fix).

How well you serve, how always sure,
In telling us the temperature.
How very seldom you're mistaken,
Although so roughly, rudely shaken.
And best, beneath a patient's tongue
(For this, indeed, your praise is sung),
How blissful, whatsoe'er the illness,
The minute that you give of stillness.

MEETINGS and Postgraduate Courses

AMERICAN COLLEGE OF PHYSICIANS: Postgraduate courses for spring 1958:

Current views in the diagnosis and treatment of cardiovascular diseases in the child and the adult, University of Illinois College of Medicine, Chicago, May 12-16

Principles and practice of internal medicine, State University of Iowa College of Medicine, Iowa City, June 2-6

Selected topics in hematology for internists, The University of Rochester School of Medicine and Dentistry, Rochester, New York, June 9-13

Internal medicine, University of California School of Medicine, San Francisco, June 16-20

For further information, write to: E. R. Loveland, Executive Secretary, 4200 Pine Street, Philadelphia 4.

HARVARD MEDICAL SCHOOL, BOSTON: Postgraduate courses for 1958:

Neurological medicine, June 2-7

General pediatrics, June 2-13

Pediatric metabolism and endocrinology, June 10-13

Internal medicine, June 16-July 26

For further information, write to: Assistant Dean, Courses for Graduates, Harvard Medical School, Boston.

NEW YORK UNIVERSITY-BELLEVUE MEDICAL CENTER, NEW YORK: Three day symposium on basal ganglia surgery for involuntary movement disorders offered in cooperation with St. Barnabas Hospital, May 15-17, at the Alumni Hall Auditorium. Sponsored by the American Rehabilitation Foundation and the Sister Elizabeth Kenny Foundation. For further information, write to: Miss Dorothy P. Frome, Office of Public Relations, 550 First Avenue, New York 16.

THE CHILDREN'S HOSPITAL, PHILADELPHIA: In collaboration with the Department of Pediatrics of the University of Pennsylvania School of Medicine, the following refresher courses will be offered during 1958:

Pediatric advances, May 26-30

Practical pediatric hematology, June 2-4

Hemolytic disease of the newborn, June 5-6

For further information, write to: Dr. Irving J. Wolman, The Children's Hospital of Philadelphia, 1740 Bainbridge Street, Philadelphia 46.

UNIVERSITY OF SOUTHERN CALIFORNIA SCHOOL OF MEDICINE, LOS ANGELES: Postgraduate courses for 1958:

Problems of malpractice in California, May 17

Office orthopedics in general practice, May 23-25

Intensive review of internal medicine, for internists, September 22-October 3

For further information, write to: Director, Postgraduate Division, School of Medicine, University of Southern California, 2025 Zonal Avenue, Los Angeles 33.

for sure antibacterial control

in urinary tract infections

mandelamine

It's effective against almost all types of urinary tract organisms... controls even antibiotic and sulfonamide-resistant bacteria. Yet, Mandelamine is *not* an antibiotic! Mandelamine won't sensitize patients... no resistant bacterial strains develop... side effects are minimal. Mandelamine is one of the safest of all drugs for prolonged use, and—happily for patients—costs far less than other antibacterial agents!

safe for long-term use for all ages

Supplied in Hafgrams® (0.5 Gm. tablets), 0.25 Gm. tablets, and pleasantly flavored Mandelamine Suspension for pediatric use. Adults take an initial daily dose of 4 to 6 Gm., and can be maintained on 3 Gm. daily indefinitely. Children need as little as 1 Gm. daily. (Mandelamine Discs, for quick identification of Mandelamine-sensitive bacteria, available from your laboratory supply house.)

Nepera Laboratories, Morris Plains, N.J

MANDELAMINE®

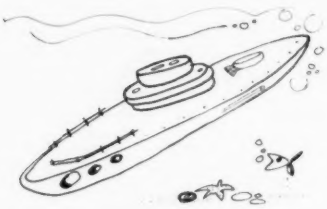
safe and effective for chronic urinary tract infections

NEPERA

DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

Feb. 5—Now reading such fine novels as "Sharks and Little Fish," by Wolfgang Ott, a tale of the German submarines during the war. In the evening to



dine with the Kahns, Millers and Samuels and played profitably at gin. Ben Samuels, who is president of the Yellow Cab, has written some excellent tales of taxi experiences, which he tells so engagingly.

Feb. 6—At my writings and in the evening with Mistress Pepys to a great benefit for Wesley Hospital, which the Angel Unit, led by Mistresses Peter Rosi and Edward Dorr, set up handsomely. Here the *Chicago Sun-Times* Book and Author Dinner was displayed for a good cause. At the speaker's table Russ Stewart said there was all of "Who's Who," and he himself was in a new picture book called "What's This?" Herman Kogan presided introducing the notables; and then spoke Willy Ley, authority on rockets, Mortimer Adler of the Great Books, who with Kelso has just written "The Capitalist Manifesto," and Max Shulman of "Barefoot Boy With Cheek" and "Rally Round the Flag, Boys." The evening bubbled with humor and wit. The auction brought spirited bidding and Jackie Leonard came over from a night club to help with the auction. Old Pepys sat with Barrett, vice-president of the Hotel Sherman chain, and Emmet Dedman, the new managing editor of the *Sun-Times,* and Roscoe Miller and Young of Northwestern. Shulman told of the man who brought the dog into the movie and explained by saying the dog was crazy over the book. Willy Ley said a trip to London would soon take three hours, one hour for flying and one at each end, to and from an airport.

Feb. 7—At noon to the annual meeting of the Brandeis University Associates, meeting Roth, Borowitz, Weinress and many other friends and here elected to the Advisory Committee. Here Kupcinet introduced Edward G. Robinson and we exchanged reminiscences of the time when I saw him play in the first week of Bart Cormack's "The Racket," some 30 years ago. Next to hear some great music at the Orchestra Hall, with Fritz Reiner conducting, and the new virtuoso from the Soviet's Gilels played Tchaikovsky. Here were again Weinress and E. G. Robinson with his new wife. Thereafter to the Main Street Book Store and met Mortimer Adler and Kelso, who signed some copies of "The Capitalist Manifesto" for me. Then home and spent the evening reading all the new medical periodicals and enjoying myself with Amy Louise and Danny while their mamma is off to meet M. Edward Davis at the Lying-In Hospital.

Feb. 8—Driving Mistress Pepys to the shops and in the afternoon came word of the birth of Ann Marie, who makes an even dozen grandchildren. At night to the home of Myron and Gertrude Kestnbaum, driving with Sam Pearlman. Here a great number of friends assembled and much fine conversation with good stories. Here were Metkow, Calvin, Himmelblau and many more and old Pepys played bridge with Portis, Mautner and Carey and did well.

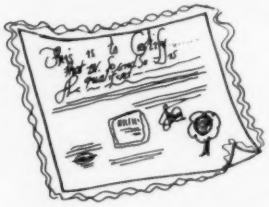
Feb. 9—Reading the new "Perspectives in Biology and Medicine," designed to communicate "heuristic ideas." In a wonderful autobiographic sketch by my teacher of 1908, C. Judson Herrick, found this anecdote:

> At a dinner meeting of the Chicago Neurological Society, Herrick was seated between J. Whitney Hall and Harold N. Moyer. Dr. Moyer chuckled as he told how he served with Dr. Hall as preceptor, stabling the horse, driving the buggy and mixing pills for more than the required two years and was impatiently waiting for the doctor's certificate of qualification for license to practice. Finally he mustered courage to ask the doctor if he thought the time had come for the certificate.
>
> "Yes, of course. I'll write it now."
>
> Whereupon Dr. Hall turned to his desk and wrote:
>
> "This certifies that Harold N. Moyer has studied medicine under my direction for more than two years. I consider him qualified for a license to practice. His moral character is as good as that of the average medical student."
>
> Young Moyer after reading the document was crestfallen.
>
> "Is that the best you can do for me, doctor?"
>
> "Humph! If you don't like it, write it yourself."
>
> The candidate took the proffered pen and wrote:

(Continued on page A-196)

JUST AS A REMINDER
4 E.N.T. products to remember!
AURALGAN
EAR DROPS
IN ACUTE OTITIS MEDIA
SAFE AURALGESIC
AND DECONGESTANT
O-TOS-MO-SAN
BACTERICIDAL—FUNGICIDAL
BROAD-SPECTRUM
THERAPY WITHOUT
ANTIBIOTICS
RHINALGAN
NASAL SPRAY
SAFE!
"NOT JUST ANOTHER
DECONGESTANT"
LARYLGAN
THROAT SPRAY · GARGLE · SWAB
FOR INFECTIOUS
AND NON-INFECTIOUS
THROAT INVOLVEMENTS
DOHO CHEMICAL CORP., 100 VARICK ST., NEW YORK 13, N.Y.

"This certifies that Harold N. Moyer has studied medicine under my direction for more than two years. I consider him qualified for a license to practice. His moral character is as good as could be expected under the circumstances."



Reading also the jubilee number of the *Atlantic Monthly* and found this fascinating report in a story called "The Glory Hole," from "Naturalist at Large," by Thomas Barbour:

Pride of possession is a curious attribute of mankind. This was brought sharply to my mind yesterday when it occurred to me to ask myself, "Why didn't Mrs. Chase *give* her gallstones to the Peabody Museum?" Many other people had, for there were a pint or more of miscellaneous gallstones in the Peabody Museum in Salem, curiously enough in the case with an old reindeer. But these were donated gallstones; it was only Mrs. Chase's that were on loan. The answer is, Mrs. Chase's gallstones were larger than any others in the whole place and she obviously just couldn't bear to part with them permanently. I thought, "Has this situation ever occurred before?" And then I remembered that not long ago I was reading the last Annual Report of the Curator of the Museum of the Royal College of Surgeons in London. This venerable institution, containing much material that was priceless indeed, suffered a direct hit from a German bomb. It was almost completely destroyed, and the story of the catastrophe was told, sadly and meticulously, by its distinguished curator. But if our friend in the street were to read this report he might be inclined to laugh heretically! Along with many terrific losses were listed the facts that the jar containing Napoleon's bowels was cracked and that the rib of Robert the Bruce was broken.

IF YOU ARE OF AVERAGE WEIGHT, IN 24 HOURS:

Your heart beats	103,680 times
You breathe	23,040 times
You perspire	1.43 pints
Your hair grows	0.01714 inch
You speak	5000 words
You use	7 million brain cells
You say "Yes, dear"	over and over
You listen to the radio and you hear	0
You smell	slightly
You cough	maybe

* * *

AMONG THE LAUGHTER

They were forming an orchestra for group therapy in the institution. One old resident was asked to join. "I don't know an oboe from a piccolo," he said. "That's all right," said the prospective conductor. "We ain't going to use none of them stringed instruments."

* * *

DEFINITIONS

Midwife—The second wife of a man who's been married three times.

Ethics—A set of principles to make sure that all contestants get an even start.

Pallbearer—A friend who's ready to give you a lift.

* * *

CONVERSAZIONE

At the lunch counter:

"Do you think if I have onion with my hamburger I'll get heartburn?"

"For 75 cents you get a hamburger; $3.00 is the charge for medical advice."

* * *

So the Friedells came and Justin and all the little ones for a fine day of fun and reading.

Feb. 10—At the desk with many new publications and read late a story by William Humphrey, "Home From the Hill," a novel of Texas, beautifully written and intricate with human emotions.

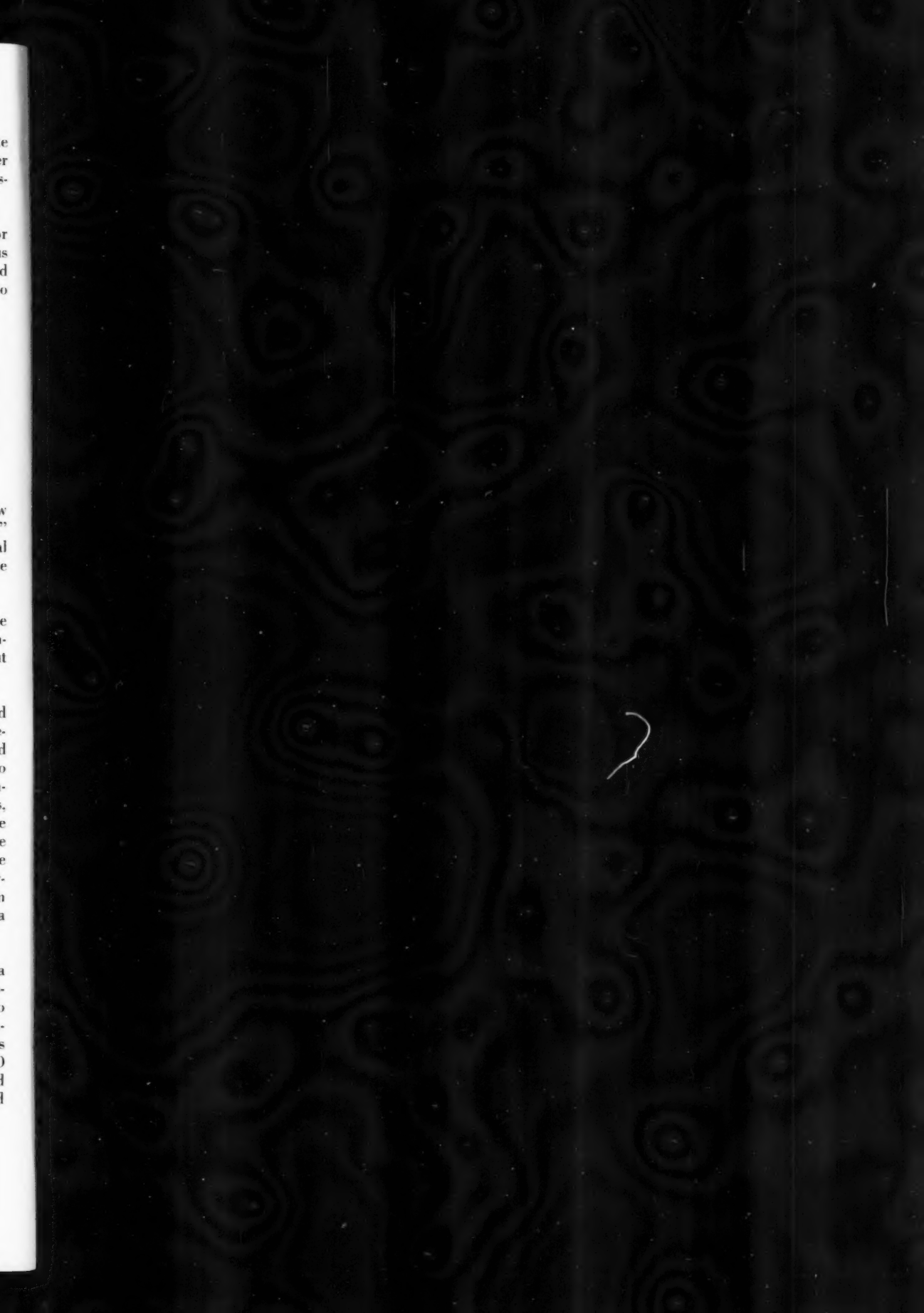
Feb. 11—Again the scrivening and at night Zola Wist invites a group to dine at the Lake Shore Club, a gathering for her sister and the prospective husband and her wedding party.

Feb. 12—At noon beset for the second time with the virus that has a habitat intestinally and chases everything else out. So

shivered and ran and read "New Directions and Modern Writing," and brushed up on experimental composition, still preferring the classic.

Feb. 13—Some more of the same. In the afternoon a long interview with Gerald Carson about John R. Brinkley.

Feb. 14—The weather turned cold with heavy snow. In the evening, feeling recovered and weighing seven pounds less, to hear the Russian violinist Leonide Kogan playing Bach, Brahms, Prokofiev, Saint-Saëns and De Sarasate, which would test the capacity of any fiddler, and he did it all so easily and with certainty as to rouse a great ovation among an audience that braved a storm to hear him.

Feb. 15—Early came Sylvia Covet and all to the Hilton Chapel at the University of Chicago where Z. W. became Mrs. Richard Hauswald. Then Mistress Pepys gave a dinner for some 30 guests, including the family and Evelyn Enge and Ed Brennan and

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